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SOME NEW APPROACHES TO THE PHYSIOLOGY OF THE THYROID*

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IT is presumptuous, perhaps, for me, a clinician, to undertake to discuss a problem in physiology. My excuse is, of course, that knowledge of the function of organs is gained not only by planned experiment, but also by taking advantage of the experiments which nature presents in the form of disease. Not infrequently nature's method has provided the earlier and sometimes the more important information. My own approach to the thyroid has been, at least of late years, more in the clinic than in the laboratory, but my colleagues have indulged in planned experiment by newer methods as well, and my purpose is to correlate those various experiences and attempt to derive a picture, however fragmentary, of thyroid function as a whole.

According to current belief, the thyroid gland has the function of manufacturing, storing and delivering to the body, as needed, its own one peculiar hormone, which I shall refer to henceforth as thyroid hormone. Whether this is an altogether correct conception, as I shall indicate later, in view of recent knowledge is open to question.

In our consideration of thyroid function as a whole we must include the manner in which the hormone acts upon its end-organs, what finally becomes of it, and how its rate of secretion is regulated. The term "end-organ" implies an analogy with the nervous system, and, indeed, such an analogy is useful. On the one hand, we have the nerve cell or neurone, with its axis cylinder conveying a stimulus neurally to an end-organ; on the other, the endocrine cell conveying a stimulus humorally, by means of its hormone, also to an end-organ. The nervous system and the endocrine system constitute two great integrating mechanisms of the body, and they are themselves coördinated one with the other.

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In the control of thyroid function the most conspicuous endocrine factor is the anterior pituitary which secretes a hormone which specifically stimulates the thyroid to make its own hormone. This has been variously called the thyreoactivator, the thyrotropic or thyroid stimulating hormone (TSH we may call it, analogous to FSH, the ovarian follicle stimulating hormone). There is also fast growing evidence that the thyroid hormone depresses the pituitary with respect to TSH secretion and thus the two glands come into hormonic balance and form a system of automatic control. To this balance, Salter [1] has given the appropriate name of "pituitary-thyroid axis" (figure 1). There are other similar axes in the endocrine system, for example, the pituitary-gonadal. So fundamental is this glandular interrelationship that I may now restate my objective as a consideration of the pituitary-thyroid axis and influences which impinge on it. The latter will include such agents as iodine, or lack of iodine, vitamins, cyanides, cyanates, sulfa compounds and the unknown agents which cause disease. The physiology which I shall lay before you will be morbid as well as normal.

Let us now review the approaches to this objective. The earliest approaches to thyroid physiology unquestionably emerged from the clinic. Because the primary action of the thyroid hormone is the calorigenic, the measurement of basal metabolic rate is the time honored and most extensively used measuring stick of thyroid function. It is a measurement of the effect of the hormone upon its end-organs. How much does the hormone increase the rate of oxidation of tissue cells? The determination of the rate of respiratory metabolism goes back to Lavoisier who, you will recall, had his head severed by the guillotine in the French Revolution, his prosecutor saying, "La République n'a pas besoin de savants." The application of such measurements to the function of the thyroid began in Germany in the 1890's when Magnus-Levy [2] measured the respiratory metabolism of patients with hyper- and hypothyroidism, and of normal persons after thyroid feeding. Since that time, particularly as a result of the impetus given it by the pioneer work in clinical calorimetry of Du Bois in this country, the determination of the basal metabolic rate has become a well nigh universal clinical procedure.

Among other now well explored approaches to thyroid physiology may be mentioned the attempts to stimulate the gland through nervous pathways [3, 4] and the observation microscopically of cyclic events in the thyroid cells and follicles.[5, 6, 7, 8, 9] The discovery by Baumann,[10] in 1896, that iodine is a normal constituent of the thyroid blazed the pathway for the biochemical approach. Milestones along this route are Kendall's [11] isolation, in 1915, of the iodine-containing amino-acid, thyroxine, and his demonstration that it exerted the physiologic properties of whole thyroid, and Harington's and Barger's [12] synthesis of this substance in 1927. Yet another approach, contemporaneous with these, is the observation of the effect of thyroid hormone upon the metamorphosis of amphibians, exploited first by Gudernatsch [13] and later by Uhlenhuth.[14]

In considering newer approaches and what has been learned by them, we may well start with those studies which have been designed to discover what actually constitutes the thyroid hormone.

You are aware that the hormones of the anterior pituitary are proteins and that those of the adrenal cortex and gonads are sterols. In the case of the thyroid, at least, it can be said that the amino-acid thyroxine, or tetraiodothyronine, given in chemically pure form parenterally in suitable dosage, will totally relieve a state of complete athyreosis. But other substances, albeit to less degree, exhibit this power. For example, if two atoms of iodine are withdrawn from the thyroxine molecule (the 3′.5′ iodine atoms of the outer ring) a compound known as diiodothyronine results. This exhibits thyroxine-like activity, but in degree only 4 per cent of that of thyroxine. Finally, diiodotyrosine, which possesses two iodine and but one phenyl group, exhibits very slight calorigenic action, but will not relieve human myxedema. It is well established that for thyroxine-like activity, that is to say, power to relieve athyreosis, the presence of iodine in the hormone molecule is indispensable. Moreover, as Salter [1] has pointed out, the high degree of activity of thyroxine is connected also with its diphenyl-ether-alanine structure.

The thyroid hormone is stored in the follicle of the thyroid gland in protein combination—the so-called iodothyroglobulin. This protein can be broken down by alkaline hydrolysis or, as Harington and Salter [15] have shown, by proteolytic digestion, into its component amino-acids. When this is done it is found that all of its iodine is divided between the two amino-acids thyroxine and diiodotyrosine.

When whole thyroid gland is fed to an athyreotic human being, it exerts a physiological activity which, as Lerman and Salter [16] have shown, is proportional to its total organic iodine content. This is rather remarkable, because, as said earlier, diiodotyrosine has but a very slight physiological activity. One would expect that whole thyroid or purified thyroglobulin would have a physiological effect proportional to its thyroxine iodine alone, but such is not the case. The diiodotyrosine iodine also is reflected in the total physiological activity. One is forced to conclude, from this seeming paradox, that in the body diiodotyrosine can be converted into thyroxine by some form of enzyme action. Such action probably cannot take place, however, unless to start with the diiodotyrosine is in some form of peptide or peptone combination. The thyroid gland is not essential to this conversion because it takes place in the thyroidless person.

Thus emerges the broader question of whether the thyroid gland is essential to thyroid-like function or merely a luxury with respect to it. Or what are the elements in extrathyroidal elaboration of thyroid hormone?

Salter's approach to this problem has been along the line of in vitro synthesis of physiologically active thyroid-like materials. Harington and Salter, having shown that by peptic digestion natural thyroglobulin can be split into active thyroxine-peptone, Salter and Pearson [17] proceeded, by suitably readjusting concentrations, solubilities and temperatures, to reverse the proc-

ess and bring about an enzymic (peptic) synthesis of an artificial protein, having thyroid-like activity, from inactive diiodotyrosine peptone. But even enzymic synthesis is not essential to the in vitro and extrathyroidal production of physiological activity, because subsequently Salter and Lerman [18] found that if indifferent protein, serum protein for example, is simply treated with compound solution of iodine in an alkaline medium without any enzymic assistance, an iodinated protein is formed which when administered in suitable dosage will completely relieve human myxedema. This is a remarkable finding and raises the further question of which came first, the hormone or the endocrine? Seemingly the endocrine is not necessary, because if our dietaries constantly contained sufficient iodinated protein we would not have need of thyroid glands. No doubt species lower in the animal scale than we, and not possessing thyroid glands, get on in this manner. We might iodinate our beef steaks before cooking them, provided we could get the beef steaks, and get on thyroidless very comfortably.

The physiological activity of such artificially iodinated protein, however, is low in terms of its iodine content as compared with that of natural iodothyroglobulin, the ratio being 1 : 4,000. This is probably because its iodine is in the form of compounds having low physiological activity and not convertible in vivo into thyroxine by the thyroidless individual.

From all this it would seem that the most plausible theory of the relation of the thyroid gland to thyroid hormone production is that the first steps in the elaboration of physiologically active material are extrathyroidal, but that the gland, by converting enzymically compounds of low activity into highly active thyroxine, serves to increase hormonic efficiency many hundred fold. As to which came first, the gland or the hormone, I think we can safely say the hormone, but in a form of low potency. The evolution of the gland, like the evolution of the cerebral cortex with respect to sensory and motor activity, has raised the whole function to one of high powered efficiency. This same line of reasoning probably applies to other endocrine glands also.*

As indicated earlier, the thyroid gland is not only a factory, but a storage warehouse as well. A consideration of the conditions under which it makes, stores or delivers its hormone, however, we may postpone until we have had opportunity to glance at the other end of the pituitary-thyroid axis. At the moment let us see what approach we have to the conveyance of the hormone to its end-organ, and how it acts upon it.

Years ago that great figure in thyroidology, the late Dr. Henry S. Plummer,[20] defined thyroxine as "an agent hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cell." He further said: "Thyroxin is active directly or indirectly in the

* Since the preparation of this manuscript the paper of Reineke and Turner [19] has appeared, in which it is reported that artificial iodinated proteins can be prepared, having several times the physiologic activity and thyroxine content of natural whole thyroid gland.

cells throughout the tissues of the body." I am not physicist enough to understand the quantum theory, in fact, I am not a physicist at all, and I am not certain that Dr. Plummer was; none the less, I think we can easily see what he was driving at, and in the main agree with him. Certainly when the thyroid hormone, be it thyroxine or other, impinges on the cell, its end-organ, energy transformation in the cell is accelerated. Or if we prefer, the vital flame is caused to burn more brightly.

The approach to the action of the thyroid hormone on its end-organs, which depends upon the measurement of gas exchange of the entire organism, that is to say the measurement of basal metabolic rate, is an old one. A newer one is that of determining the effect on the gaseous metabolism of isolated tissues in vitro by means of the Barcroft-Warburg apparatus. By this latter method several approaches are available. One may, for example, give hormones to animals and then sacrifice and determine the metabolism of isolated tissues, or one may excise tissues and expose them to substrates to which hormones have been added.

By the former method it has been found that the oxygen consumption of isolated tissues (QO_2 it is generally called) of animals made thyrotoxic by thyroid administration is higher than that of untreated animals, except thyroid tissue, which is lower.[21, 22, 23]

Salter and Craige [24] have used the action of patients' plasma on the QO_2 of mouse liver as a test of thyroid function. The plasma of thyrotoxic patients raised, that of myxedematous ones lowered the QO_2 relative to the normal control. The authors point out that the basal metabolic rate of the subject is vicariously reflected in the metabolic rate (QO_2) of the liver tissue exposed to his plasma. They, therefore, used the term VMR—vicarious metabolic rate—and found a very good agreement between it and the BMR.

The approach to hormone action in isolated tissue by adding hormone directly to the substrate bathing it is well exemplified by the work of Canzanelli and Rapport.[25] These investigators, in one series of experiments, determined the effect of thyroglobulin and derivatives of it on the QO_2 of guinea-pig liver and of rat liver. Pure thyroxine had no effect on the QO_2 of either tissue. Thyroglobulin, on the other hand, markedly increased the QO_2 of each. Diiodothyronine had a variable but on the whole negligible effect and diiodotyrosine had no effect on guinea-pig liver and consistently depressed the QO_2 of rat liver. From these observations the authors concluded that thyroxine is not the thyroid hormone and that the hormone is either thyroglobulin or an integral part of it.

If thyroglobulin is to be looked upon as the hormone, however, one would expect to find it in the circulating blood en route from thyroid to end-organ. This, however, has not been done. On the contrary, its absence from the blood stream has been established by Lerman,[26] who produced a thyroglobulin antiserum by injecting human thyroglobulin into rabbits "which was able to detect by precipitin reaction minute amounts of thyroglobulin in solution, namely 0.08 to 0.15 mg. per 100 c.c." By means of this reaction Lerman

could find no detectable thyroglobulin in the blood of normal persons or of myxedematous persons or of thyrotoxic persons either before or after iodinization. The only time Lerman could detect appreciable amounts of thyroglobulin in the blood was when he obtained samples from the thyroid vein toward the end of an operation during which the surgeon had been handling the thyroid. Evidently at operation some intact thyroglobulin is milked into the blood stream, but Lerman was able to show that after operation it disappears very rapidly. Either it is destroyed or fixed by the tissues. From this work of Lerman's together with that of Canzanelli and Rapport, we may draw the conclusion that thyroid hormone travels from the thyroid to its end-organs in a form lower than the protein level, and that it acts upon its end-organ in a form of higher level than that of the amino-acids. It may both travel and act in the form of a polypeptide or peptone. Certainly there is thyroxine iodine in the blood, and if not in the form of thyroglobulin, it is probably in the form of split products thereof.

The blood can be studied as to its thyroid hormone concentration by fractioning its total organically-bound iodine. This approach has been used by many investigators, often, because of technical difficulties, with conflicting results. Now, however, with improved methods dependable figures can be got, and Bassett, Coons and Salter [27] have shown that the protein-bound iodine of the blood can be used as a dependable index of circulating thyroid hormone. In studying patients with either hyper- or hypothyroidism there was an even closer correlation between this factor and the estimate of thyroid function based on symptoms than between the latter and basal metabolic rate.

Canzanelli, Guild and Rapport [28] have further shown, in a more recent study, that thyroglobulin directly applied will also raise the QO_2 of guinea-pig testis, kidney and heart muscle. There appeared, however, to be a ceiling beyond which increasing concentration of hormone had no additional effect.

In contrast to this Galli-Mainini,[29] of Buenos Aires, who spent the years 1940 and 1941 working in our laboratory, obtained evidence that thyroglobulin depresses the QO_2 of guinea-pig thyroid tissue. If this result is correct, and I may say that it remains to be confirmed—although it is in agreement with the in vivo work which I have cited—it signifies that the thyroid hormone has an effect upon the cells which make it opposite to that upon indifferent cells of the body. Moreover, there is rapidly increasing evidence that the thyroid hormone depresses the anterior pituitary with respect to the production of thyroid stimulating hormone. Thus it may well be that within the pituitary-thyroid axis we have two self-regulating or automatic apparatuses, in each of which rising thyroid hormone production leads, through elevated thyroid hormone blood level, to decreased thyroid hormone production (figure 2). In one case the hook-up is thyroid to pituitary to thyroid, in the other thyroid to thyroid. It is to be doubted that either the thyroid cell or the pituitary cell is exempt from the general thyroid hormone action of stimulation, but in the case of these two tissues there may be in

addition a specialized action of inhibition which more than cancels that of stimulation.

When we approach either the elaboration, or better perhaps the finishing of a hormone by an endocrine, or the action of a hormone on its end-organ, we get nowadays at once into enzyme chemistry, for these processes are certainly enzymic, and unfortunately I am no more enzyme chemist than physicist.

However, we all perhaps now know that oxidation in a living cell, in contrast to that in a Bunsen burner, is a complicated series of reactions involving the tossing about of hydrogen and oxygen atoms from molecule to molecule under the influence of enzymes with a resulting oxidation at body temperature, instead of a simple and violent union of oxygen and hydrogen with liberation of great heat and without benefit of enzymes or catalysts, as is the case in the Bunsen burner. On this oxidative enzyme system of the cell the thyroid hormone somewhere impinges to cause acceleration.

Of course, there are other actions of thyroid hormone than that of increasing the rate of metabolism of the cell or the whole organism, but these may be looked upon as associated or by-effects of the fundamental oxidative action. Among these may be mentioned its action on growth, metamorphosis and the differentiation of tissue (all of which are accelerated), and also upon the distribution and exchange of water, salts and colloids of the body, upon hepatic glycogen stores (which are depleted under an excess of the hormone), upon the circulation (which is accelerated), upon the nervous system (which is rendered more irritable) and others.

Let us now go to the other end of the pituitary-thyroid axis and consider TSH and its action. Of its structure, beyond that it is protein, we know but little. However, it is possible to extract protein material from the anterior lobe in such a way that the other characteristic actions, such as gonadotropic, adrenotropic and growth promoting, are largely eliminated and only the thyroid stimulating remains. One can, in other words, obtain a fairly pure preparation of TSH. With such preparations many interesting experiments can be performed.

For example, material of this kind, when administered parenterally (being protein it is digested when given by mouth and rendered inert), will cause the thyroid epithelium to increase in height and show cytologic evidence of increased secretory activity. It also will cause an increase in QO_2 of thyroid tissue either in vivo or in vitro. It will bring about discharge of stored colloid from the follicles and, in the whole organism, elevation of metabolic rate, and all that goes with a greater output of thyroid hormone. At least it will call forth such responses for a time, but ultimately a refractory stage is reached in which the organism may swing to a hypothyroid level despite the continued administration of TSH. Such development of refractivity could be due either to the exhaustion of the thyroid or to the development of some type of antagonist to TSH.

It is obvious that the thyroid is the chief end-organ of the pituitary thyrotropic hormone. As one of my colleagues has put it, TSH plays the rôle of thyroid hormone to the thyroid gland. The question arises, however, are there other (non-thyroid) end-organs directly affected by TSH? Probably there are; however, but little is known of them. In the development of exophthalmos, either experimental or spontaneous, TSH may be a factor. In animals, exophthalmos has been observed to follow the administration of TSH, and this effect is more pronounced in thyroidectomized than in intact animals. Also, as I shall indicate a little later, in certain cases of

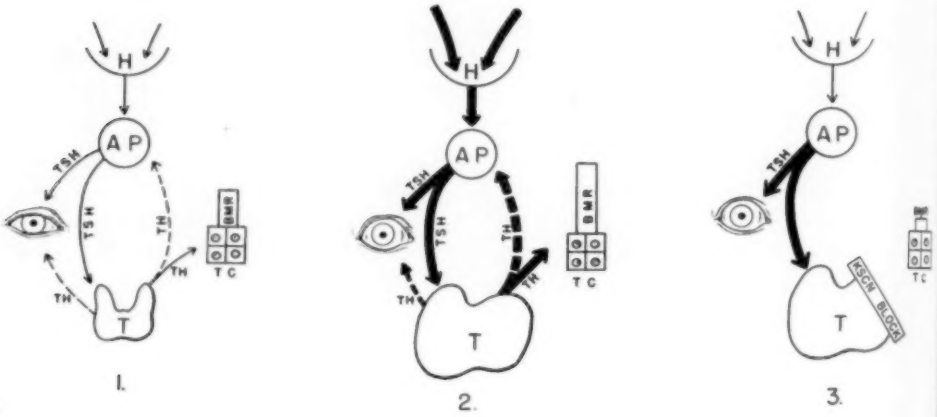

FIG. 1. The pituitary-thyroid axis.

(1) *In the normal individual.* Nervous influences impinge on the hypothalamus, H, which in turn stimulates the anterior pituitary, AP. The anterior pituitary stimulates the thyroid, T, humorally, by means of its hormone, TSH. The thyroid thus stimulated produces its hormone, TH, which stimulates tissue cells, TC, to increase their oxidative processes, BMR. Also TH inhibits AP, indicated by broken line, thus comes about the balance. A secondary effect is indicated upon the eye. TSH promotes exophthalmos, TH inhibits it.

(2) *In Graves' disease.* Hypothalamic stimulation of AP may be increased as shown by heavier arrows. Increased TSH causes hyperfunction and hyperplasia of T. Increased TH raises the BMR of TC, but at the same time there should be some inhibition of AP. TSH, it is believed, also promotes exophthalmos, which even increased TH cannot altogether offset. This interpretation is admittedly hypothetical. The primary event could be in hypersensitivity of thyroid to TSH or hypersensitivity of tissue to TH, or hyposensitivity of AP to inhibition by TH. More data are needed to settle these points. The present interpretation is offered as a first approximation.

(3) *Under the influence of cyanate.* The primary event here seems to be the imposition of a block which prevents the completion of TH. This absence of TH causes stimulation of AP with increased production of TSH, which causes hyperplasia of T, but because of the block, no production of TH. The BMR of TC accordingly falls and the unopposed TSH causes exophthalmos. (With apologies to F. Albright.)

Graves' disease in human beings in which thyrotoxicosis is minimal or absent and the eye involvement maximal, an excess of TSH can be demonstrated in the urine. How TSH is related to the swelling of orbital tissues, which causes exophthalmos, is quite obscure, but that it has something to do with it and that this action is independent of the thyroid, seems most likely. In other words, TSH, or some derivative of it must have other end-organs than thyroid tissue.

The action of TSH on thyroid cells has been studied by Rawson [30] and his co-workers by means of tissue culture technic. Explants of rabbit thyroid were bathed with fluids containing known amounts of TSH. After a suitable period of incubation, they were withdrawn and subjected to bioassay for thyrotropic activity. The remarkable finding was that all such activity had disappeared. The thyroid cells had inactivated their stimulator. The effect of other tissue explants on TSH was also studied. Lymph node and thymic tissue caused partial inactivation; adrenal, kidney, ovary, pancreas, parathyroid, testis, spleen and stomach mucosa caused none.

Subsequently, Rawson [31] was able to show that the inactivated TSH could be partially reactivated by heating, in the presence of mild reducing agents, the fluid which had been exposed to the action of thyroid.

Thus it appears that when thyroid is stimulated by TSH the hormone is inactivated, but it is not destroyed. Its activity can be restored by simple reduction.

In 1936, Hertz and Oastler [32] by bioassay, had found thyrotropic activity in the urine of certain patients with myxedema, but had failed to find it in the urine of either normal or thyrotoxic persons. Rawson,[31] however, repeating this work has been able to show thyrotropic activity in all these urines after heating. Evidently TSH is present in all, but in the normals and thyrotoxics chiefly in the inactivated form.

Rawson [33] has also made explants of tissue from human thyroids, both normal and abnormal, removed at operation. The normal thyroid tissue was obtained at operation upon parathyroid lesions. The surgeon obligingly snipped off a bit of thyroid tissue also for explantation. Exposure of known quantities of TSH in solution to these various explants disclosed that the glands taken from persons in a thyrotoxic stage of Graves' disease had a greater power to inactivate TSH than normal glands. Thyroid tissue from persons with non-toxic nodular goiter had no TSH inactivating power at all. It appears that in the toxic phase of Graves' disease the thyroid gland is under increased stimulation by TSH and that in this process an increased amount of TSH is inactivated and excreted in the inactivated form in the urine, from whence it can be recovered by artificial reactivation.

One would like to learn the precise nature of the reaction between TSH and its end-organ, the thyroid cell. Is it similar to that of the thyroid hormone on its end-organ cell? Some light is being thrown on this question by work now in progress in our laboratory by Graham and Rawson. It has been found by these workers that the inactivation and reactivation of TSH can be carried out entirely in the test tube, without any interposition of thyroid cells, by the use of mild oxidizing agents for inactivation and mild reducing agents for reactivation. This suggests that when TSH encounters thyroid tissue it becomes inactivated by an enzymic oxidation reaction. Inactivation of the hormone seems to be an accompaniment of its stimulating action on its end-organ.

The next new approach to thyroid physiology which I should like to discuss with you is that which employs radioactive iodine as an indicator. As far as I am aware, the first paper on the use of tagged iodine as a means of studying thyroid function is that of Hertz, Roberts and Evans,[34] which appeared in 1938, a publication from the Thyroid Clinic of the Massachusetts General Hospital and the Physics Department of the Massachusetts Institute of Technology. The idea of such a method originated with Hertz after he had listened to President Carl T. Compton of the Massachusetts Institute of Technology speak at the Harvard Medical School on what aid physics can render to biology and medicine. Similar work was started shortly afterward by Hamilton and Soley [35] in San Francisco, and by Leblond [36, 37] and his coworkers, in Paris and later in Rochester, New York.

The principle involved is that the thyroid has a specific avidity for iodine, obviously because iodine is an indispensable ingredient of its hormone, and that, if iodine can be labeled, a new method of studying thyroid physiology is available.

Tracer studies by means of tagged atoms are now being employed in a very wide range of physiologic and biologic problems. Usually the tagging is accomplished by making an atom temporarily radioactive by bombardment of a suitable target with neutron or deuteron beams. Another method of tagging is by using stable isotopes of the substances in question, such as deuterium or heavy water. The method of radioactive labeling has the great advantage over older chemical methods that the course of an atom, or molecule into which a radioactive atom has been incorporated, can be followed through the body in vivo and its disposition in tissues, or even cells, can be determined after excision with far greater precision than any chemical method could achieve. Hamilton, Soley and Eichorn,[38] for example, allowed slices of thyroid which had collected radioactive iodine to take their own photomicrographs. Examination of such pictures betrayed the exact location of iodine in the tissue even down to the cytologic level.

In their earlier work, Hertz and Roberts [34] used a short-lived (26 minute half period) isotope of iodine, derived from a radium-beryllium source. With this material, experiments of short duration only could be accomplished, and only animals studied, because excision of tissue was necessary for detection of iodine distribution. Much was learned, however, even thus and very soon other isotopes of iodine with half periods of 12.5 hours, eight days and 13 days became available. These were produced by bombardment with the beam from the cyclotron.

The original purpose of the animal studies was to discover the laws governing the collection of iodine by normal and hyperplastic thyroid glands and to establish the normal and pathologic behavior of the thyroid toward iodine under various circumstances. There was the hope, too, that such studies might yield information which would later permit the use of radioactive iodine for therapeutic purposes. This hope has now been realized.

In experiments on rabbits receiving iodine intravenously, it was found

that the percentage collection from any given dose reached a maximum within ten minutes, and that this was not exceeded for periods of collection as long as several days. The normal thyroid was found to collect up to 80 times the quantity to be expected from uniform diffusion into the general tissues of the body. In thyroids made hyperplastic by giving the animal TSH, cyanates or placing it on a diet high in cabbage, it was found that the relative concentration of iodine in the gland might reach several hundredfold. Another finding of interest was that the percentage uptake of iodine by the thyroid increases as the size of the dose decreases. Relatively more of a small dose is collected than of a large one; but, if the smaller dose is adequate, the total amount collected from it will be the same as that collected from larger doses. There appears to be a ceiling for iodine collection by the thyroid gland. Thus the thyroid very rapidly takes up iodine from even very small doses to the point of saturation and after that lets it pass on to the organism as a whole. The effect of a previous dose of ordinary iodine on the subsequent collection of a labeled one of standard size was found to be a reduction which was related to the size of the pretreatment dose. That is to say, if the gland had previously been well filled with iodine, its collection of a subsequent labeled dose was consequently diminished. This is the result which would be expected from what had previously been learned of the thyroid's iodine-collecting behavior. This information was secured by the method of multiple labeling, that is to say, using isotopes of different half lives which could be distinguished one from another in the body. This principle of multiple labeling, incidentally, affords an important new approach to thyroid and other physiology.

In further extension of their work, Hertz and Roberts [39] compared the effect of TSH administration in rabbits upon uptake of radioactive iodine, thyroid cell height, relative size of the thyroid and basal metabolic rate. It was found that cell height, relative thyroid size and basal metabolic rate vary essentially in parallel under the influence of TSH. The collection of radioactive iodine, given in a standard dose, follows these factors up to the point at which the ceiling for such collection is reached. Beyond that it cannot increase.

The effect of pretreatment with iodine causes the final values for all factors reached after TSH to be lower than if no such pretreatment with iodine had been given. Hertz and Roberts concluded that the effect of giving TSH is initial stimulation of the thyroid cells to collect iodine followed by involution (colloid storage in the follicles), if iodine treatment is given. However, if one continues TSH administration without iodine, exhaustion of the thyroid ultimately takes place, that is to say, loss of its capacity to collect iodine.

When sufficiently active preparations were available, Hertz and Roberts [40, 41] extended their studies to human beings. By means of Geiger counters placed over the thyroid it was possible to follow the deposition of labeled iodine in the gland and its subsequent departure. Blood levels of

tracer iodine and its elimination in the urine were also followed. In the case of 22 thyrotoxic patients, whose goiters were removed by the surgeon, it was possible, with the collaboration of Salter, to determine the chemical distribution of labeled iodine as between thyroxine-like and non-thyroxine-like fraction of the total organic iodine content.

As in the case of animals, it was found that the hyperplastic thyroid (in this case that of Graves' disease) collects more iodine than the gland of the healthy person. Also, as in animals, the relative uptake is largest at low dosage levels. The hyperplastic thyroid in the thyrotoxic phase of Graves' disease may collect initially 80 per cent or more of a dose of 2 mg. The rapidity of collection of iodine by the thyroids of either man or animal is such as to support the view that the time required is merely that taken by the iodine to reach the thyroid. Having been collected, radioactive iodine is observed to disappear slowly, in the case of the hyperplastic gland more rapidly than in the case of the normal one. Analysis of the thyroid after operation showed that the radioactive iodine was increasingly in the form of the thyroxine-like fraction the longer the time between administration and analysis. No chemical analyses could be made on normal human thyroids, because we have not yet felt justified in removing them. Total thyroidectomy for heart disease might afford an opportunity, but that procedure has largely fallen into disuse.

We may perhaps summarize the tracer studies by saying that in both man and animal iodine is taken up by the thyroid to its saturation point as fast as it reaches the gland. The ceiling is greater in the case of hyperplastic than in normal glands. In the thyroid the iodine is used, probably, partly to convert the tyrosine of thyroid protein into diiodotyrosine, and partly to convert diiodothyronine into thyroxine. The actual disposition will depend on the preëxisting state of iodination of the amino-acids already in the gland. When more iodine is supplied to the thyroid than it can utilize, it is allowed to pass by in the blood stream and in due course is excreted. There is no evidence of a storage depot of importance for iodine in the body other than the thyroid.

The release of iodine from the thyroid, other than that which merely passes through it having been refused collection, must be in whatever form the thyroid hormone is delivered to the blood. I have previously indicated that the evidence points to this being somewhere between the amino-acid and protein levels.

When, in Graves' disease as in animal experiments, a dose of ordinary iodine was given previous to the labeled, the collection of the latter was consequently decreased. This is perhaps what would be expected.

The iodine requirement of hyperplastic glands is undoubtedly greater than of normal glands because they are making, or trying to make, more of the iodine-containing hormone. In the uniodinized case of Graves' disease the thyroid is poor both in total quantity of stored protein and also in the degree of iodination of its protein. The work of Hertz, Roberts and

Salter [40] shows that such a gland cannot become saturated with iodine by accumulating small amounts, but tends rather to make it into hormone and release it.

Let us now consider the pituitary-thyroid axis from the point of view of agents or influences which may affect it (figure 1). TH and TSH are inherent parts of the axis itself. Iodine is a necessary ingredient of the hormone, and supplying it when it is deficient is bound to have important repercussions. Of other agents I wish to discuss briefly cyanides, cyanates, and sulfa compounds, and of influences, the influence of disease.

It has been known for some years, chiefly as a result of the work of Hunt,[42] Chesney [43] and his collaborators, and Marine [44] and his, that cyanides alter thyroid function, in fact, that they may produce goiter and at the same time cause hypothyroidism.

A little over a year ago, a patient [45] appeared in our clinic who had been taking potassium thiocyanate for about a year as treatment for essential hypertension. Recently he had rapidly developed a goiter, which on physical examination proved to be so hard as to suggest malignancy. At the same time he began to complain of symptoms quite characteristic of hypothyroidism, and still further to confuse the picture, we observed that he had slight exophthalmos. We succeeded in obtaining a biopsy of the thyroid, and it turned out to be wildly hyperplastic. The thought at once was that the cyanate had caused this paradoxical picture, namely, hyperplastic goiter with hypothyroidism, and it was decided, therefore, to note the effect of omitting it. Upon omission, the goiter rapidly disappeared and the basal metabolic rate rose from minus 18 to plus 5, the blood protein-bound iodine from 2.1 to 5.0 gammas. A similar case was presently reported by Kobacker,[46] and we were told of a third by Blumgart.

Evidently cyanides, and seemingly cyanates, or sulphocyanates as well, may cause a situation in which the thyroid is thwarted in its attempt to supply its end-organs adequately with its hormone. Two possibilities emerge: first, that the end-organs' responsiveness is depressed by the agent with the result that the thyroid undergoes hyperplasia and pours out an excess of its hormone; and second, that the agent acts upon the thyroid itself and in some way prevents the completion of hormone manufacture. That cyanides suppress tissue oxidation lends weight to the end-organ theory, but the weight of more recent evidence favors the view that the action is on the factory which turns out the hormone. Lerman, for example, gave to a patient with myxedema who was being maintained in a steady state at BMR minus 10 to minus 15 by a daily ration of thyroid gr. 1½ gr., 15 a day of potassium sulphocyanate for six weeks, in the meanwhile thyroid being continued as before. No fall in basal metabolic rate occurred, which indicated that potassium sulphocyanate does not oppose the action of thyroid hormone upon its end-organ. Cyanate goiter patients, on the other hand, taken off the drug, show a drop in basal metabolic rate when it is resumed. Also blood

iodine falls even ahead of basal metabolic rate. The inference is that the action is upon their thyroids. The myxedema patient having no thyroid capable of function failed to respond.

It is to be noted further that iodine will prevent cyanide goiter, and as it has been known since the early work of Marine that iodine want will cause thyroid hyperplasia, the effect of cyanide might be interpreted as being to raise the thyroid's iodine requirement, or, if you prefer, to lower the point at which iodine want becomes manifest in cytological and functional expression.

Marine has claimed that the thyroid made hyperplastic from any cause may be made to involute by giving an excess of iodine, but quite recently it has been shown by the MacKenzies,[47, 48] in Baltimore, and Astwood,[49, 50] in Boston, that the sulphonamide drugs will cause a type of hyperplastic goiter accompanied by hypothyroidism, preventable by giving thyroid, but not preventable by giving iodine. Astwood has found that feeding rats on a large series of compounds containing the thiourea nucleus and also certain aniline derivatives will do the same. The use of such substances, together with that of cyanides and cyanates, constitutes, I feel certain, an important new approach to thyroid physiology.

If we liken the elaboration of thyroid hormone by the thyroid to that of "flivvers" in the assembly line at River Rouge, then it appears that these various agents, like cyanides, cyanates, sulfa drugs, thioureas, and so forth, impinge at various points to throw the line out of gear and frustrate the completion of a perfect hormone. Because the effects of cyanides and cyanates are preventable by iodine, whereas those of sulfa drugs and so forth are not, it is to be presumed that they block the assembly line at different points.

Finally the study of naturally occurring disease is a fruitful approach to thyroid physiology. I have recently discussed the nature of Graves' disease with the Vanderbilt Chapter of Alpha Omega Alpha.[51] The chief point I should like to make about it at present is that here is another influence which impinges on the pituitary-thyroid axis to upset it, or force it into a new and pathological type of equilibrium.

What the morbid influence is which causes Graves' disease, no one knows with certainty. At present it seems likely that nervous impulses which strike it via the hypothalamus-pituitary route are important causative factors. The consideration of immediate interest is that the thyroid becomes hyperplastic and presumably turns out an excess of thyroid hormone, so much so in fact that it becomes drained of its reserve supply of hormone stored in its follicles as iodothyroglobulin. Some writers have claimed that the situation is one of thyroid failure, but the only sense in which the thyroid fails, so far as I can see, is that it fails to get iodine enough to iodinate all the hormone it would like to make under the influence of morbid stimulation.

When iodine is given in Graves' disease, as you all well know, some very dramatic events take place. The hyperthyroidism rapidly declines and the

thyroid undergoes involution. If the hyperplastic thyroid of Graves' disease were like that of cyanate goiter, one would expect, under the influence of iodine, that more hormone would be produced and the basal metabolic rate would increase. But such is not the case. Seemingly in Graves' disease the action of iodine is complex. Iodination of thyroid protein is undoubtedly accelerated, but at the same time the high concentration of iodine in the blood throws the reaction in the direction of colloid storage in the follicles rather than delivery of more hormone to the blood. The gland fills up with well iodinated colloid, but, if administration of iodine is continued, finally the saturation point is reached and then at last an excess of hormone spills over into the blood stream. Iodine in a sense imposes, as do cyanide, cyanate or sulfa drugs, an impediment to the delivery of thyroid hormone, but at a quite different point. Instead of obstructing the assembly line, it may push the finished product into the warehouse instead of permitting free distribution to the body—economic or biologic.

I shall now recapitulate and at the same time attempt a synthesis.

We can imagine perhaps a remote ancestor emerging from the primordial ooze and discovering, rhetorically of course, that his protoplasm would

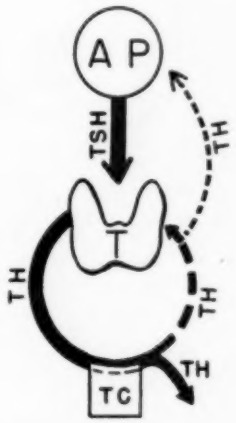

FIG. 2. Galli-Mainini's conception of the pituitary-thyroid axis.

The anterior pituitary, AP, stimulates the thyroid, T, by means of its hormone, TSH. T then makes its hormone, TH, part of which decays in the act of stimulating tissue cells, TC. Another portion of TH remains in the blood stream and inhibits T directly, also AP. Thus the double regulation comes about.

transform energy more rapidly if he iodinated some protein and used it as a respiratory catalyst. There being plenty of iodine in the sea water, this offered no great difficulty. The iodination of protein took place as a simple chemical reaction. The iodine was attached probably as diiodotyrosine or diiodothyronine.

After the passage of some aeons the vertebrate stage was reached and then more efficient systems were evolved. Enzymes—iodases—appeared and promoted more rapid transformations. A finishing off factory in which a high powered respiratory catalyst, thyroid hormone, could be fabricated from the lower iodinated forms was obtained by converting a digestive gland into an endocrine. This involved the loss of its duct. It became, in fact, ductless. The cells of this so-called thyroid gland learned to collect iodine from the blood stream with great avidity and rapidly, through the mediation of enzymes to incorporate it into the thyroglobulin molecule which could then be either stored in the follicles or split up and delivered to the blood stream.

Regulatory devices came into being (figure 2). Probably they are but manifestations of mass action. A low concentration of thyroid hormone in the blood causes the reaction to go in the direction of increased production of hormone. When a certain blood level is reached the reaction goes in the other direction and hormone storage in the follicles occurs. Self-regulation thus emerges. The delivery of hormone to the blood is probably in the nature of a splitting down of thyroglobulin: the storage in follicle, of building up—a reversible enzyme controlled reaction.

But nature was not satisfied with such a simple regulation. A master endocrine was likewise evolved, which would receive stimuli from the nervous system and transmit them on humorally to the endocrine [52]—a superior type of regulation became imposed upon the thyroid—and the pituitary-thyroid axis came into being. Of the evolution of the pituitary's thyroid stimulating hormone, I suppose we know next to nothing. We don't even know its chemical constitution beyond that it is a protein. However, we do know that it exists, and somewhat about how it works.

As Rawson has shown, it impinges on the oxidative enzyme system of the thyroid cell, perhaps in the capacity of a co-enzyme, and in so doing occasions acceleration, not only of cellular oxidation, but of cellular secretory activity as well. Presumably the oxidative enzyme system of the thyroid cell, and its secretory system, are part and parcel of a single functional cellular organization. Under the impact of TSH the thyroid cells not only increase their function, but undergo such structural change as is demanded by this increased function. In the act of causing such stimulation, TSH becomes oxidized and physiologically inert, and is excreted in that form in the urine. But it can be reactivated by reducing agents, and its physiological activity restored. When the thyroid is rendered incapable of responding to TSH through disease, then TSH appears in its active form in the urine.

Surfeiting the thyroid with, or depriving it of iodine produces results which throw light on its physiology. Iodine want, as Marine [53] showed years ago, causes hyperplasia for a time, but with gradual failure of hormone production and finally involution and exhaustion of the thyroid. It is a hyperplasia of frustration. Excess of iodine in the normal has little or no effect. The thyroid uses what it needs and lets the rest pass by.

In the thyrotoxicosis of Graves' disease, however, iodine has a remarkable effect. Here again the thyroid is hyperplastic, but is putting out excess of hormone. The cause of this hyperactivity is unknown. It could be due to a morbid stimulation of the thyroid (as by an excess of TSH) or it could be the result of an abnormal sensitivity of the thyroid to normal stimulation. Still a third possibility is that the thyroid hormone's end-organs have gone hay-wire and call for extra hormonic stimulation. I think the first of the three is the most probable. In any event, what happens when one gives iodine is obvious enough. The thyroid traps an unusually large amount of iodine, it stores thyroglobulin in its follicles and the basal metabolic rate and thyrotoxicosis decline. At the same time less TSH is inactivated and more excreted unchanged in the urine. Seemingly raising the concentration of iodine in the blood acts as a barrier to the discharge of hormone to the body, probably by reversing in some fashion the reversible reaction involved. After a time the barrier may be forced and thyrotoxicosis, in some measure, return.

Why iodine in excess does not have a comparable effect on the normal gland, I do not know. The element of morbid stimulation is apparently necessary to the Graves' type of response.

The effects of cyanides, cyanates, sulfa compounds, and so forth, on the pituitary-thyroid axis, and the fact that all can be forestalled by thyroid, but not all by iodine, opens up a new and important approach to thyroid physiology. Presumably these agents interrupt the enzyme systems of the thyroid, some at one point, others at other points. The result in all, is that hormone output is blocked and the resulting hypothyroidism causes stimulation of the pituitary, which in turn causes hyperplasia of the thyroid. In any case thyroid, and in that of cyanates and cyanides, iodine, will prevent this pituitary stimulation.

I am sure as I now close that you will have the feeling that our knowledge of thyroid physiology is very fragmentary. That is true, of course, but there are some beautiful leads to follow—for example, the rate of manufacture of TSH by the pituitary, the manner in which the pituitary is stimulated to make it, the manner in which the pituitary is inhibited by thyroid hormone, and also whether iodine as such affects the pituitary or whether it is the diphenyl-ether-alanine nucleus which is important. The questions, moreover, of whether TSH has other end-organs than the thyroid epithelium, and how thyroid hormone acts on its end-organs, are likewise intriguing. Finally, I venture to predict that more study of comparative endocrinology or even of paleoendocrinology will be productive. I hope that some of you will tackle some of these problems.

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RADIO-PHOSPHORUS—AN AGENT FOR THE SATISFACTORY TREATMENT OF POLYCYTHEMIA AND ITS ASSOCIATED MANIFESTATIONS; A REPORT OF A CASE OF POLYCYTHEMIA SECONDARY POSSIBLY TO THE BANTI'S SYNDROME *

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Polycythemia is a disease of unknown etiology characterized by a chronic course and a marked increase in total blood volume over the normal, with an absolute increase in the total number of red blood cells (and often of white blood cells and of platelets).

In a previous paper [1] evidence was presented that marked clinical and hematological improvement occurred in six cases of polycythemia, following administration of radio-phosphorus (p^{32}). Those six patients have been maintained in essentially complete clinical and hematological remissions for nearly two years.[2] Four of the six patients have required no radio-phosphorus additional to that described in the previous paper, whereas one † has had one intravenous injection and another has had two courses of three injections each of radio-phosphorus. With the above evidence, plus the evidence presented in this paper which describes the treatment of an additional 11 cases of polycythemia, it would appear that radio-phosphorus is probably the most conveniently administered and the most satisfactory therapeutic agent known at the present time for the treatment of polycythemia. Others [3, 4] have expressed somewhat similar opinions.

Materials and Technics

All of the radio-active phosphorus ‡ solutions were injected intravenously. The variations in dosages were due to the inability to obtain radio-phosphorus at regular or specified intervals of time because of conditions beyond our control, and do not represent a planned régime. The majority of the total dosages varied between 7 and 11 millicuries. As was pointed out in the first paper,[1] since the average life span of the human red cell is approximately 60 to 100 days, the first significant hematological responses occurred about 60 to 100 days after the first injection of radio-phosphorus. It is interesting to note that Head [21] observed three remissions in a typical case of poly-

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† This patient, whose disease of polycythemia was well controlled with radio-active phosphorus for three years, began losing weight in January 1943 and died five months later of hypernephroma with metastases (J. H. Lawrence, personal communication).

‡ Radio-phosphorus was produced by the Berkeley cyclotron and was forwarded by Dr. John H. Lawrence.

TABLE I

Treatment of Polycythemia with Radio-Active Phosphorus

Patient	Date of Admission	Chief Complaints and their Duration	Treatment-Response before & during admis.	Physical Findings on Admission	Lab. Findings on Admission: Hg(%)	R.B.C(mill.)	W.B.C(thous)	Plat.(thous)	Retic.(%)	Hematocrit	Bl. Vol.(cc/kilo)	Sternal Aspiration M.C.V.
1. E.Bro. Female Age 58 English School teacher 99 lbs.	11-20-34	Pain in upper left quad.-4 mo. Generalized exzematoid itching rash-Acne Urticata Polycythemia-2 yrs. Vomiting-2 yrs. Dandruff-2 yrs. Weakness & fatigue-2 yrs. Staggering-1 yr. Intense headaches-2 yrs. Insomnia-2 yrs. Arthritis ?-1 yr.	Salves & ultra-violet irradiation. Sedatives X-radiation-unsatisfactory Phenylhydrazine therapy started	Thin, emaciated, florid individual Generalized maculo-papular eruption Noticeable plexis of enlarged veins on arms and legs Spleen-6cm. below costal margin Liver-3cm. Palms of hands red	112	8.5	32.0	500	2.0	71		
	3-3-39	*Same as above-Plus:* Pain-(boring in nature) in hands and feet. Arthritis worse ?	Phenylhydrazine-poor response Venesection	*Same as above-Plus:* Spleen extended inferiorly for 10cm.	118	7.5	18.0	542	0.4	67	112	97
	11-19-41	*Same as above.*	Phenylhydrazine-fair response Venesection Fowler's solution	*Same as above*	100	5.5	21.0					
	12-4-41	*Same plus-* Lumbar pain bilaterally Bleeding from kidneys Bleeds easily when she cuts herself Cramps in fingers and toes		*Same-plus:* Spleen reached iliac crest Wt.-110 lbs.	99	5.03	25.0	300	1.0	69	110	Ess. Normal
2. S.Geg. Female Age 62 Scandinavian Dressmaker 126 lbs.	7-23-38	Dizziness-8 yrs. Precordial pain-1 yr. Pain in "left side"-1 yr. Shaking movements of hands & feet-6 yrs. Incontinent at times Arthritis ? Sleepiness	Venesection Phenylhydrazine started	Thin, poorly developed, but florid. Mucous membranes deep purple Spleen 3cm. Liver 2cm. Inguinal & axillary lymph nodes palpable. Palms of hands red.	130	11.5	15.0	200				
	12-10-40	*Same as above-Plus:* Mental confusion Weakness	*Same-Plus:* Fowler's solution-poor response	*Same-Plus:* Spleen-8 cm. Liver-4 cm.	128	11.0	12.0	134	2.6			
	10-12-41	*Same as above-Plus:* Headache Bloody diarrhea Pains in hands and feet	Phenylhydrazine-fair response	Emaciated Veins of arms & legs markedly rominent	100	8.5	6.0			69	180	69
3. E.Le G. Female Age 60 American Schoolteacher 110 lbs.	3-20-43	Weakness-progressive-1 yr. Floridness-20 yrs. Father & grandfather very florid. Father died following craniotomy for relief of "cerebral hemorrhage"	Phenylhydrazine-poor response	Small, slender, very florid. Conjunctiva & oral membranes markedly conjested. Palms of hands very red. Prominent veins. Spleen-2cm below left costal margin.	162	7.8	19.9	156	0.4	75	166	Ess. Normal 100
4. M. Mac C. Male Age 64 American Brick layer 143 lbs.	1-10-43	Gnawing pain in abdomen. Dizziness-1 yr. Floridness-20 yrs. Single episode of unconsciousness 1 day before admission. Father & grandfather apparently had polycythemia. Pt remembers both as very florid & in later yrs grandfather had to be bled every 2 mo. to maintain good health	None	Thin, nervous, florid individual. Palms of hands red. Veins prominent	149	9.5	11.9	328	0.5	75	204	Ess. Normal 79

TABLE I (*Continued*)

Date	Amt. of radio-active Phosphorous admin IV in millicuries	No. of mo. after initial treatment with Radio-active Phosphorous	Physical Findings	Laboratory Findings: Hg(%)	RBC(mils.)	WBC(thous.)	Plat(thous.)	Retic.(%)	Hematocrit	Bl. Vol(cc/kilo)	Sternal Aspiration	M.C.V.	Comments
12-4-41	2.8												
12-10-41	2.8												
12-15-41	1.5												
	7.1 Total												
No other medication Advised not to eat eggs or red meat.													
		1-14-42 1 mo.	Rash clearing Spleen 5cm	83	4.19			0.3	45				No pain in upper left quad.
		4-13-42 4 mo.	Rash about gone Neither spleen nor liver palpable	63	3.5	5.5							No complaints
8-24-42	1.5												
	8.6 Grand Total	8-29-42 8 mo.	No skin lesions or symptoms Neither spleen nor liver palpable	78	4.25	5.0	120	0.2	35	107			Patient jubilant - first time she has felt well in 8 yrs. Gained strength & wt. (now 116 lbs.) No rash or itch. Prominence of veins disappeared
		10-13-42 10 mo.		72	4.4	4.4					Ess. Normal		Working first time in 8 yrs. Excellent appetite Age 64
		12-22-42 12 mo.		69	3.4	6.4	108						
		1-11-43 13 mo.		75	3.9	7.4			35	86		102	
		4-22-43 16 mo.		70	4.05	7.1							Feels better than in past 10 yrs. Weight - 138 lbs.
		5-20-43 17 mo.		75	4.16	7.2	150		39	104		97	Works daily. No complaints Weight 139 lbs. Age 65
11-1-41	3.5	12-9-41 1 mo.	Spleen-2cm Tongue-less red. Lymph nodes not palpable.	102	8.24	5.0			57				First time in 7 years patient feels like staying awake after 8 P.M.
11-8-41	2.0												
11-15-41	.8												
	6.3 Total	2-7-42 3 mo.	Mucous membranes normal color	97	6.4	4.0		0.2	46			77	Gastric hemorrhage thought to be due to ruptured varicies
Patient advised not to eat red meat or eggs		6-24-42 7 mo.	Neither spleen nor liver palpable	80	4.73	4.8	126		27	78			
		8-12-42 9 mo.	Prominence of veins has disappeared.	66	4.65	5.3							Feels fine. No complaints. Wt 146 lbs. Age 66 Good appetite.
		12-1-42	*Patient was seen by a physician elsewhere, who gave her iron echinacea, and quinine. We estimate that she took between 7 and 10 gms of iron during Dec.*										
1-9-43	2.0	1-9-43 14 mo.		108	7.7	6.9							
3-10-43	1.2	3-24-43 16 mo.	Spleen - 3 cm below costal margin.	118	9.5	10.	64						Complains of dizziness & edema of ankles. 500 cc. blood withdrawn.
4-7-43	2.0												
4-14-43	.8	3-31-43											500 cc of blood withdrawn
4-21-43	.4	4-7-43		102	8.15	6.0	86	1.4	55	133		66	500 cc of blood withdrawn
5-1-43	1.6	4-14-43											500 cc of blood withdrawn
	8.0 Total	4-21-43 17 mo.		91	8.9	9.5							500 cc of blood withdrawn
		5-1-43	Spleen no longer palpable.	87	5.6	5.4			45	91			Feeling much better Wt. 144 lbs. No dizziness or edema of ankles.
6-8-43	3.0	6-8-43 19 mo.		83	5.3	3.5						64	Works daily. No complaints Wt 144 lbs. Age 67
	17.3 Grand Total												
3-20-43	1.8												
3-22-43	1.5	5-1-43	1½ mo.		122	7.1							Less florid - Regained strength.
3-24-43	.4												
4-17-43	3.	5-22-43	2 mo. Spleen not palpable. Veins no longer prominent.	116.	5.67	3.7	9.0						Nearly normal complexion
5-17-43	1.6						86	0.2					No complaints. Very happy about marked physical improvements. Wt 112 lbs.
	8.3 Total	6-12-43	3 mo.	106	5.23	6.50	116		60	91	Hypoplastic	107.	Normal complexion Works daily without fatigue
2-1-43	4.0	4-7-43	2 mo.	99		6.8							Gained nearly 50 lbs. Wt 189 lbs. Voracious appetite. Feels very well. No complaints.
2-3-43	1.5					5.4							
2-24-43	2.3												
3-10-43	1.5	5-1-43	3 mo.	87	5.5	7.0					Ess. Normal		
4-7-43	.6												
4-21-43	.24	6-5-43	4 mo. Spleen not palpable. Veins no longer prominent.	71	3.95		156	0.3	35	91		89	Lays bricks daily without complaint Complexion normal. Wt. 186 lbs.
5-1-43	1.1				5.6								
	11.24 Total												

TABLE I (*Continued*)

5. M. Muir Female Age 30 American Housewife 120 lbs.	8-19-40	Abdominal mass. L upper quad. Dizziness, Headache, Stumbling All of 3-4 months duration.	Phenylhydrazine not tolerated Fowler's solution.	Sclera & conjunctiva injected. Emaciated & florid. Veins prominent. Spleen 6cm. Bl. Pr. $\frac{?}{60}$	122 9.2 15.0			64		74			
	12-17-40	Diagnosed Multiple Sclerosis and polycythemia	Course of X-radiation & given- Dec. 1940, April, 1941, Oct. 1941		135 5.2 7.0			56		100			Res. Normal
	10-5-42	Same as above:		Same as above:	129 7.7 12.0		204	60		230 (?)			
6. H. Melz. Male Age 58 Hebrew Tailor 147 lbs.	2-3-43	Weakness, Dizziness, Abdominal pain, Indigestion. All of 5 yrs. duration	Frequent venesection Often as once a mo during the year preceding admission. Last venesection 2 days before adm. Phenylhydrazine	Thin, emaciated but pale individual Dark complexioned Prominent veins on arms and legs.	51 6.4 12.0		300	.7 32 92		50			
7. R. Hou. Male Age 54 German Janitor 136 lbs.	8-23-41	Mass & pain in upper left quadrant, preventing pt. from lying down for 6 mo. Weakness & fatigue. Loss of weight - 30 lbs during previous yr. Vomited large amounts of blood in 1939 & again March 1941. Had not worked for 2 yrs. because of weakness & severe attacks of pain in "L side", probably due to repeated splenic infarcts.	4 courses of x-radiation since 1937. Phenylhydrazine previous year. Fowler's solution No satisfactory response to any of these.	Thin emaciated, florid. Prominent veins in arms & legs. Spleen reached iliac crest. Infarct present. Spleen tender. Liver 3cm. Tongue beefy & red. Palms of hands red.	99 8.6 31		220	1.9 54 112		57			Hyperplastic Normal Diff.
8. A. Mus. Male Age 56 Ukranian Janitor 121 lbs.	4-24-42	Gnawing pain in abdomen. Nausea & vomiting - 1 yr. Weakness - 2 yrs. Wt. loss - 20 lbs. in 1 yr. Headache - 2 yrs. Had not worked for nearly 2 yrs. because of symptoms	Had received "Stomach ulcer treatment" for past year.	Thin, emaciated, florid. Prominent veins in arms & legs. Mucous membranes deep purple Spleen & liver - 3cm.	134 11.0 10		242	74 210		65			Res. Normal
9. J. Nag. Male Age 41 American U.S. Navy 122 lbs.	4-13-42	"Weakness & heaviness" - 2 yrs. "Fullness in head", headache - 2 yr. Attacks of pain in upper left quadrant - 1 yr. Indolent ulcers of rt. leg - 2 yrs. R.B.C. over 8 million - 2 yrs. Unable to work - 2 yrs.	X-radiation and phenylhydrazine both made patient sick.	Thin, emaciated, florid. Prominent veins on arms & legs. Large indolent ulcer - 3 cm Mucous membranes deep purple Liver - 2 cm.	138 8.5 13		220	1.2 75		320 (?)			Res. Normal
10. I. Udell Male Age 60 Hebrew Glassgrinder 178 lbs.	7-8-42	Weakness & headache - 8 yrs. Burning feet & painful toes - 2 yrs. Unable to pick up small objects with fingers. Has not worked for 4 yrs.	X-radiation Ultra-violet radiation to skin. Venesection. Poor response	Plethoric, well nourished, ruddy. Mucous membranes purple hue. Large toes red & very tender. Spleen 2 cm.	163 10.0 10		252	0.4 70 250		70			Res. Normal
11. O. Wet. Female Age 51 Amer. Negro Maid 100 lbs.	5-4-42	Weakness - 8 yrs. Fatigue - 8 yrs. Headache - 3 yrs. Pains in hands & feet - 2 yrs. Backache - 2 yrs. Insomnia - 2 yrs. Nervousness - 8 yrs.	X-radiation - small amts. Ultra-violet irradiation of auto-transfused blood. Fowler's solution Poor response	Thin, emaciated colored maid. Mucous membranes purple hue. Prominent veins in arms & legs Spleen just palpable.	126 11.0 14		104	76 200		76			Res. Normal

cythemia vera which occurred in each instance, three months following application of radium.

Of the 11 patients, six were white males (two Russian Hebrews), four were white females, and one was a colored female. Each patient had had polycythemia from two to eight years or more before therapy with radioactive phosphorus was instituted. The course of polycythemia varies markedly.[5] All had received many types of therapy previous to radio-phos-

TABLE I (*Continued*)

10-9-42	3.65	1-11-43	3 mo.		78					No complaints except for unsteady gait.
10-26-42	1.2				3.69					
	4.85 Total	3-18-43	5 mo.	Spleen not palpable Normal complexion	74	4.6				
		5-6-43	7 mo.		80	5.3	6.6			
						10.3	5.0			
2-5-43	1.0	4-26-43	2 mo.	Spleen 3 cm. below left costal margin	61	5.5	7.8			Wt. 148 lbs.
4-28-43	.55									
	1.55 Total									
		6-9-43	4 mo.	Spleen 3 cm. below left costal margin						Wt 148 lbs. T.B. Splenitis (?)
10-2-41	3.7	11-12-41	1 mo.	Spleen 8 cm. No tenderness	98	5.0	3.3			First time patient could lie
10-9-41	2.8								71	down in bed for 6 mo.
10-16-41	1.0									Patient started working.
	7.5 Total	12-12-41	2 mo.	Spleen 4 cm. Prominence of veins disappeared.						
No other medication. Advised not to eat eggs or red meat.		12-25-41		Pt. was feeling fine. No complaints. Wt. 157 lbs. Worked daily without discomfort.						
		12-26-41		Pt. suddenly died elsewhere following large gastric hemorrhage. Post-mortem could not be obtained.						
4-15-42	1.3	6-3-42	2 mo.	Gained 5 lbs. Neither spleen nor liver palpable.	135	9.1	3.0	61	78	No "stomach trouble". Started to work. Voracious appetite.
5-2-42	7.3									
5-25-42	2.4	8-5-42	3 mo.	Gained 20 lbs. Tongue normal color. Prominence of veins disappeared. Normal complexion.	91	5.9	6.0	41	Ess. Normal	No complaints. Feels "wonderful" Working hard & does not tire. Wt. 141 lbs.
	11.0 Total							135		
No other medication. Advised not to eat red meat or eggs.		1-11-43	7 mo.		82	4.1	7.2	40	81	
		6-11-43	14 mo.		85	4.4	7.0	86		Wt. 145 lbs. Has worked daily for 1yr. without complaints.
4-13-42	1.5	8-8-42	4 mo.	Leg ulcer completely healed. Neither spleen nor liver palpable. Prominence of veins disappeared. Normal complexion.	85	4.38	9.0	44	91	Pt. feels fine, but still complains of some weakness. Wt. 138 lbs.
4-17-42	2.6							110		
4-22-42	2.2								Ess. Normal	
8-8-42	4.5									
	10.8 Total									
No other medication. Advised not to eat red meat or eggs.		10-22-42	6 mo.		68	3.86				Works daily but complains of weakness
		1-18-43	9 mo.		77	4.39				Works daily without complaints.
		3-3-43	11 mo.		80	4.14	7.0			Feels that he is "completely cured"
7-15-42	2.6									
7-17-42	5.6	8-12-42	1 mo.	Spleen not palpable. Pain & redness in toes disappeared. Normal complexion.	122	7.6	5.0	57	68	No complaints, no headaches Wt 180 lbs.
8-7-42	3.1						14.2	195		
	11.3 Total									
No other medication. Advised not to eat red meat or eggs.		9-23-42	2 mo.		80	5.23				No complaints. Moved to another city.
5-4-42	9.3	5-21-42	3 wks.		126	10.92	+		76	
5-21-42	2.2									
	11.5 Total	8-29-42	4 mo.	Neither spleen nor liver palpable. Prominence of veins disappeared.	61	3.47	+	140	91	Pt. states that she feels better than in past 20 yrs. No headaches. Sleeps well. Voracious appetite. Wt. 128 lbs.
No other medication. Advised not to eat red meat or eggs.								0.8		
								3.1		
		10-13-42	6 mo.		66	4.62		99		

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phorus, such as roentgen-radiation, ultra-violet irradiation to skin or to auto-transfused blood, Fowler's solution, phenylhydrazine, venesection, etc., but none had had satisfactory remissions following such treatments. None had been treated with lead compounds,[6] or spray roentgen therapy.[14] The symptoms varied widely, from those cerebral or spinal in character such as lethargy, dizziness, staggering (multiple sclerosis syndrome), incontinence, etc., to those involving the gastrointestinal tract (symptoms of duodenal and

stomach ulcers and gastric bleeding), the vascular system (tender congested toes, thromboses, varicosities, prolonged bleeding tendencies), the cutaneous system (eczema, acne urticata polycythemic, indolent leg ulcers), the osseous system (arthritis), the urinary system (bloody urine) and the reticulo-endothelial system (splenic infarcts). Two of the patients (cases 3 and 4) presented evidence that polycythemia had probably existed in their families for the two preceding generations. Familial polycythemia is probably identical with polycythemia vera.[7]

Ten of the 11 patients were thin and emaciated * with prominent enlargement of the superficial veins of the arms and legs. All had marked congestion of the mucous membranes, and the hands of each patient (one exception) had decidedly red palms. With one exception secondary polycythemia, such as sclerosis or syphilis of pulmonary vessels, bronchiectasis, tuberculous or syphilitic splenitis, congenital atresia of the aorta, chronic heart lesions, poisonings, etc., were ruled out by histories, by physical examinations, and by hematological, roentgenological, serological and cutaneous tests. Dameshek and Henstell[8] have shown that an iron-poor diet prolonged remissions following venesections of patients with polycythemia. Iron-free diet as a treatment for polycythemia was first proposed by Erhlich.[9] Reznikoff et al.[10] showed in both normal and polycythemic individuals and Cruz et al.[11] in dogs that the iron of old or discarded red cells is reutilized in the formation of new hemoglobin. Because of such information all of the patients were placed on a meat-and-egg-free diet after the first injection of radio-phosphorus.

The pipettes and counting chambers used on these cases were standardized by the United States Bureau of Standards. The hematological technics were those used universally. The blood volume studies were made by the use of 1 per cent Congo red solutions. Wintrobe sedimentation tubes were used to determine the hematocrit levels. Sternal punctures were made by the technic described in 1937[12]; and the sternal marrow findings of the 17 cases of polycythemia presented then were essentially the same as those of the seven patients (before treatment) presented in this paper.

Results

The clinical and hematological findings before and after treatment with radio-phosphorus of 11 cases of polycythemia are presented in table 1.

In table 2 are listed the sternal bone marrow findings before (in eight cases) and after (in eight cases) treatment with radio-phosphorus.

After treatments with radio-phosphorus the patients usually gained weight, developed unusually good appetites and had clinical and hematological remissions. The changes that occurred in associated conditions follow:

* This feature was emphasized by F. Parkes-Weber.[33]

	Total nucleated cells per cu. mm. in aspirated marrow fluid (thous.)	Myeloblasts	Neutrophilic myelocytes	Eosinophilic myelocytes	Neutrophilic metamyelocytes	Polymorphonuclear neutrophiles	Polymorphonuclear eosinophiles	Polymorphonuclear basophiles	Lymphocytes	Plasmocytes	Megakaryocytes	Megaloblasts	Erythroblasts	Normoblasts	Reticulo-endothelial cells	Cells in mitosis	Peripheral red blood cell levels (millions)
E. Bra.																	
3–14–39 before p^{32}	50.2	2.2	12.3	1.	21.9	46.6	.67		1.67	.33	.33	2.	3.33	7.33		.66	7.5
8–30–41 after p^{32}	35.	.3	23.6		20.3	18.6	2.		7.			2.	1.6	23.3	.6	.3	4.2
6–28–43 after p^{32}	23.	1.0	18.3	1.3	23.3	26.6	2.6		3.3		.6	1.3	2.3	18.3		.6	3.6
S. Geg.																	
6–28–43 after p^{32}	10.		18.		25.	23.5			5.0			.5	2.0	25.0	1.5		5.4
LeGrand																	
3–24–43 before p^{32}	86.	.6	18.6	2.6	11.6	16.6	2.6	1.03	3.3	.3	1.3	1.3	10.3	29.3			7.8
6–12–43 after p^{32}	12.	1.3	6.6	1.0	10.3	31.3	1.0		8.3	2.0	.3		3.3	33.0	1.0		5.2
R. M. Mc																	
1–19–43 before p^{32}	45.	.5	7.5		15.0	43.0	.5	1.5	5.5	.5				26.			9.5
6–24–43 after p^{32}	24.	.3	20.0	2.0	14.0	26.6	.6		6.6				.3	29.3			3.8
H. Mei																	
1–19–43 before p^{32}	13.		11.0	2.0	20.0	36.0	3.0	1.0	2.0		1.0	2.0	1.0	21.			6.4
6–23–43 after p^{32}	34.	.3	20.0	.6	13.3	24.1			1.6		.3	2.0	1.6	35.3			5.4
8–10–43 "	115.	2.0	17.	1.3	20.	16.3			3.3		.6	1.3	9.0	27.0			6.0
R. Mou.																	
9– 3–41 before p^{32}	108.	2.6	12.6	.33	15.6	40.	1.3	1.6	2.6			.33	2.3	20.			8.6
M. Mui																	
10–8–42 before p^{32}	74.	.66	16.	1.3	32.6	18.6	4.6		3.6			.33	2.3	18.	1.0	1.0	7.7
A. Mus.																	
5– 7–42 before p^{32}	37.	1.	11.	1.6	16.	18.	2.6	1.	4.	2.33	.33	3.6	3.3	34.	.1	1.3	11.0
8–27–42 after p^{32}	32.	.6	19.	.3	11.6	16.3	1.		6.6				3.3	40.	.3	.6	4.6
6–16–43 after p^{32}	133.	1.0	12.0	2.6	15.0	18.3	.6		1.6	.3	.3	2.3	9.6	35.6		1.0	3.8
J. Nagel																	
6–21–43 after p^{32}	21.	.3	11.0	2.6	23.3	26.0	.3		5.0		.6	1.0	.6	28.3	.6		3.9
O. Wel.																	
5–22–42 before p^{32}	26.	1.3	25.	.66	13.3	10.	.33		7.3	.66			4.6	35.3	.66	.66	11.0
8–30–42 after p^{32}	100.	.33	20.	2.	16.3	13.3	.33		5.	1.3	.66	.66	6.6	33.3			3.4
7– 7–43 "	93.		15.	2.	25.	19.	1.		1.6			1.	2.6	31.	.3	1.6	3.7

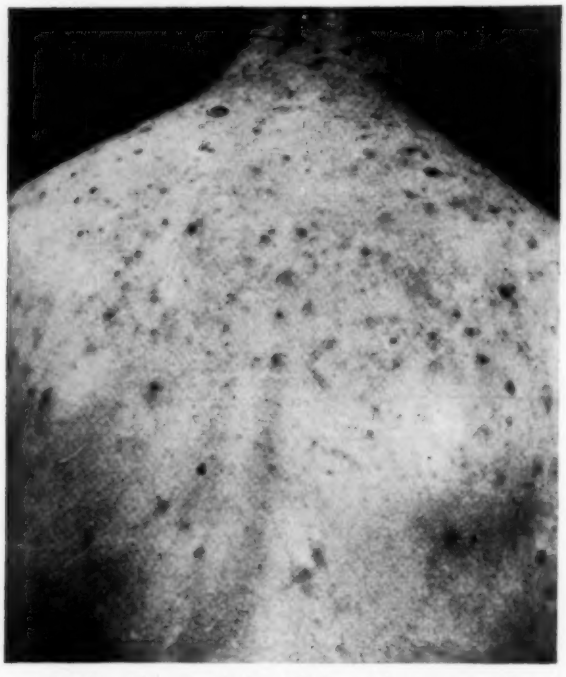

FIG. 1. The reproduction (by permission of the authors—see reference 12) of a photograph of patient 1 published in 1939. The lesions, which were of eight years' duration, were described as acne urticata polycythemic and were responsible for much itching, burning and scaling to the patient.

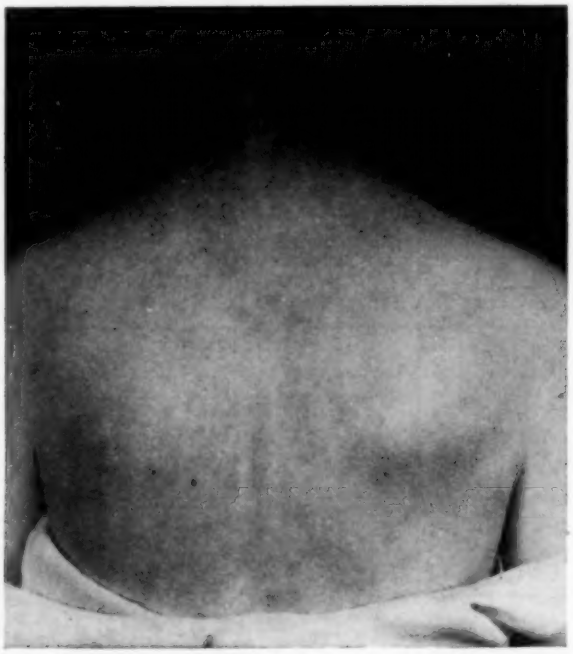

FIG. 2. Photograph of same patient in 1942 after treatment with radio-phosphorus. Patient is now free of all cutaneous discomfort.

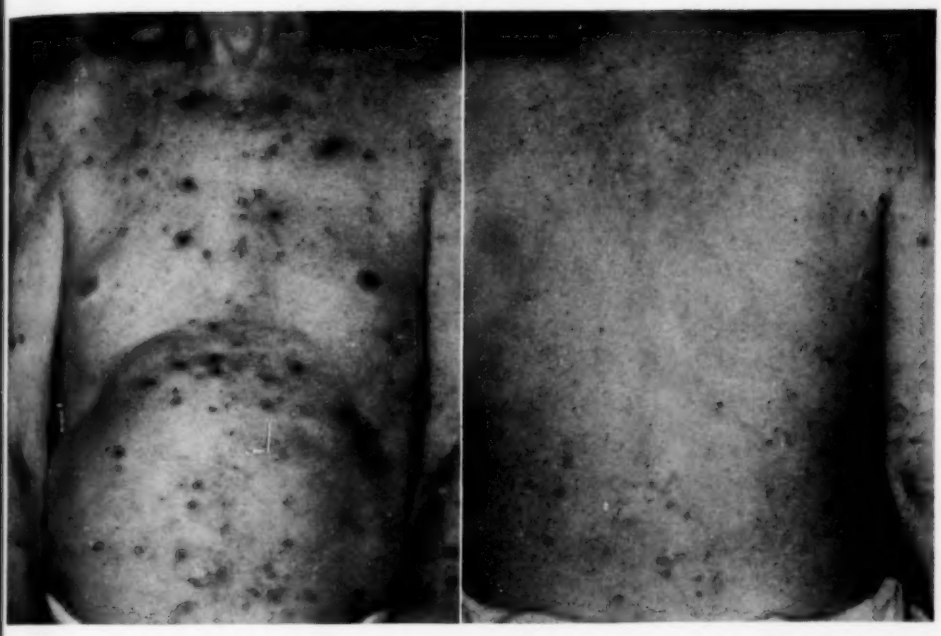

FIG. 3. Photograph of patient suffering from chronic dermatitis herpetiformis of six months' duration before administration of radio-phosphorus. Patient complained of intense itching, burning and scaling.

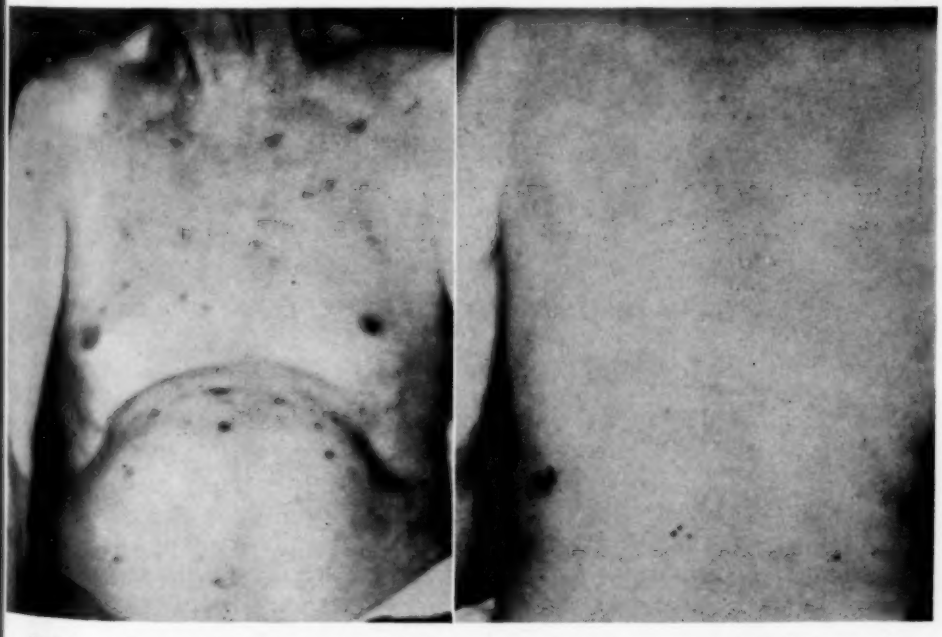

FIG. 4. Photograph of same patient 30 days after p^{32}. All symptoms had disappeared 80 days after p^{32}—no evidence of the former condition could be observed.

a. Skin Conditions. Figures 1 and 2 show the skin of the back of patient 1 before and after therapy with radio-phosphorus. The skin lesions of this particular patient were described in minute detail and termed acne urticata polycythemic by Weidman and Klauder.[18] The lesions which had existed for eight continuous years were generalized and caused almost unbearable itching and burning. Scaling of skin and scalp (dandruff) was profuse. All of these symptoms disappeared completely after treatment with radio-phosphorus, and have not returned for over a year.

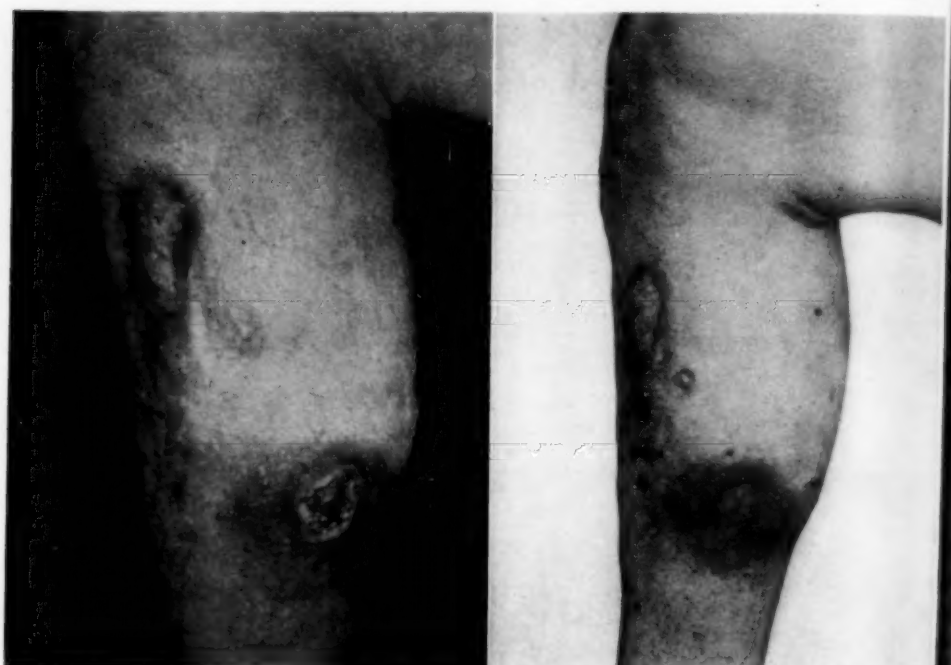

FIG. 5. (*Left*) Photograph of ulcers of leg of patient 9 before radio-phosphorus therapy. These ulcers had been weeping for a period of over two years. No therapy had benefited the patient.

FIG. 6. (*Right*) Photograph of the same leg shown in figure 5 three months after radio-active phosphorus had been administered. Lesions are scarred and no longer weeping.

The improvement of the skin lesions may not have been a result of an improvement of the polycythemic syndrome since another patient, who did not have polycythemia but who had similar lesions (as to appearance, distribution, symptoms and refractoriness to treatment) for a period of six months (diagnosed as chronic dermatitis herpetiformis by the Division of Dermatology, Jefferson Hospital) improved equally well following treatment with radio-phosphorus. Within one week after administration of 2 Mc. of p^{32} the intense itching had disappeared. Figure 3 shows the lesions before, and figure 4 shows the lesions four weeks after injections of p^{32}. Within less than 80 days the lesions had completely disappeared.

We have had two patients with Hodgkin's disease suffering from intolerable generalized itching of the skin who derived complete relief following therapy with p^{32}. The radio-phosphorus probably did not alter the course of the Hodgkin's disease.

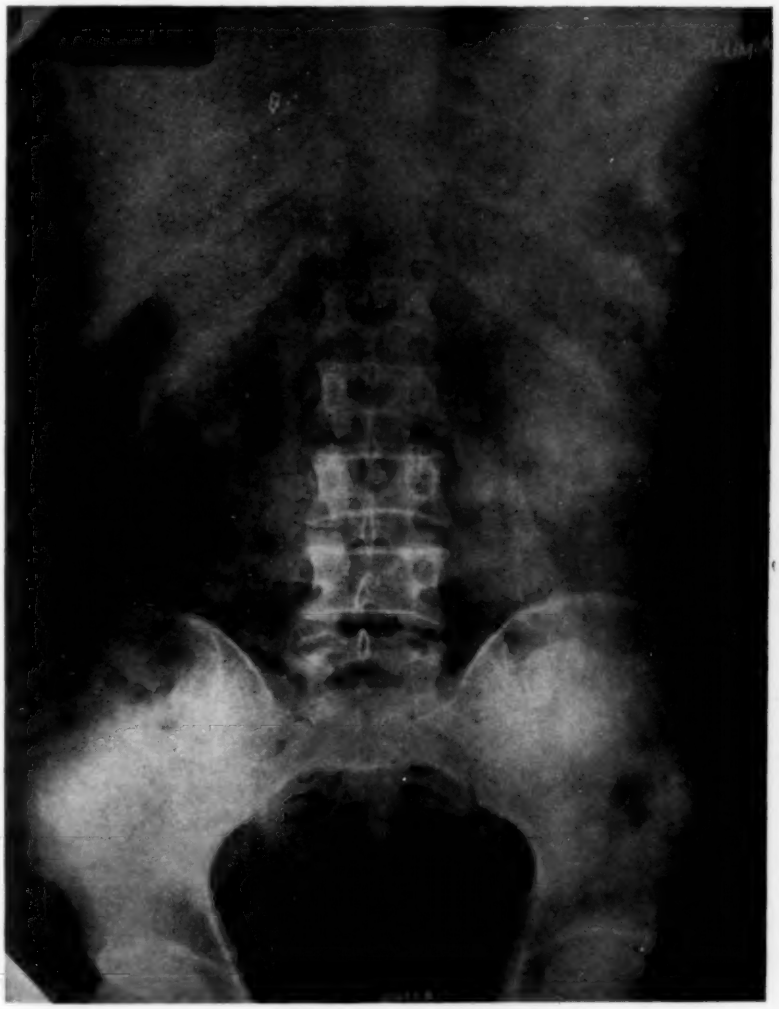

FIG. 7. *Case 6.* Focal areas of calcification of the spleen.

Patient 9 had had chronically weeping indolent leg ulcers for over two years with every type of therapy failing until radio-phosphorus was administered. The weeping ceased and within two months after p^{32} administration the ulcer healed, leaving a pigmented scar (figures 5 and 6). A year later the scar had become softer and continued to remain asymptomatic.

b. Mean Corpuscular Volume. The values of the mean corpuscular volume of nine of the 11 cases were below normal, indicating that the red blood

cells of patients with polycythemia are smaller than normal. In eight of nine cases studied the red cells became larger after treatment with p^{32}. Case 2 had a relapse following the unauthorized ingestion of large doses of iron, and simultaneously the mean corpuscular volume decreased. As soon as a remission was reëstablished, however, the mean corpuscular volume became nearly normal.

c. Coagulation Time. The coagulation time of polycythemic blood is abnormally prolonged, and patients bleed readily following minor cuts. This symptom disappeared following therapy with p^{32}.

d. Gastric Hemorrhage. Four of the 10 cases had been informed elsewhere that they had gastric ulcers and three of the patients had had gastric hemorrhages before therapy with p^{32}. Case 7 had had large exsanguinating gastric hemorrhages one and two years before treatment with p^{32}. However, after the blood findings had returned to normal levels and the patient was asymptomatic following treatment with p^{32}, a severe fatal gastric hemorrhage occurred. Case 2 also had a gastric hemorrhage after p^{32} had been started. This patient had a relapse after taking iron and was brought back into a state of remission following phlebotomy and additional treatment with p^{32}, without the occurrence of gastric hemorrhages. For the third case (No. 6) of gastric hemorrhage see addendum.

e. Bone Marrow Findings (*see table 2*). The differential marrow findings in cases of polycythemia are rather similar to those of normal individuals. Strangely the percentage of the erythropoietic elements is often decreased in number. It is apparent, therefore, that in polycythemia greater quantities of marrow throughout the body become hyperactive. Since the marrow findings (both the total nucleated count and differential) in pretreated cases of polycythemia are nearly within the limits of normal, it is logical that the findings would not be significantly altered following therapeutic doses of radio-phosphorus.

Discussion

The 11 patients reported here plus the six reported previously [1] have stated that the remissions following radio-phosphorus were satisfactory and that no other therapy had given equally satisfactory remissions. It must be brought out here that none of these patients had received spray roentgen therapy which according to many authors [14, 15, 16] gives excellent remissions in polycythemia. The mechanism of these two types of therapy may be similar. Radio-phosphorus concentrates in the bone marrow and continuously bombards such tissues for days.[17, 18] Both p^{32} and roentgen radiation probably decrease red blood cell production by retarding mitosis of normoblasts in early prophase.[19, 20] (Radio-phosphorus is not a red blood cell lytic agent, as is phenylhydrazine, because neither jaundice nor increased excretion of urinary urobilinogen has been observed following administration.) In both types of treatment (radio-phosphorus and spray roentgen radiation) the period of irradiation (by beta particles) is prolonged, which

may be the effective factor. We hope to be able to study these two types of therapy, including the measurement of iron intake and excretion in patients with polycythemia.

Conclusions

At the present time, in our experience, radio-phosphorus is the most convenient and satisfactory therapeutic agent for the treatment of polycythemia and its associated manifestations.

Addendum

Patient H. M. (No. 6 on table 1) had had five severe gastric hemorrhages (hospitalized elsewhere) during the seven years preceding treatment with radio-active phosphorus. Because he was so fearful of gastric hemorrhages, he gave monthly a pint of blood to the Red Cross during the twelve months preceding his admission to Jefferson Hospital. During that same year he had had several attacks of syncope associated with a drop in blood pressure to as low as 70/40. When we first saw the patient we obtained the history of polycythemia (by letter from a hospital where he had previously been studied), and we felt that the marked hypochromia and microcytosis (hemoglobin 51 per cent, red blood count 6,500,000, and mean corpuscular volume 50) observed on admission were sequelae of the monthly blood donations. However, after months of weekly determinations of blood levels, no changes were noted and we gave the patient iron (adequate doses of ferrous sulfate) expecting that the hemoglobin and red blood cell levels would rise immediately, as occurred in case 2. During the period of the administration of iron, the patient developed two attacks of syncope (a week apart), and the systolic pressure fell into the 70's. In addition, the administration of iron was not followed by a significant elevation in the red blood cell and hemoglobin levels. One of us (L. A. E.) began to suspect the patient had polycythemia, secondary to some other process, and sent the patient to the roentgen-ray department as a possible case of quiescent primary tuberculosis of the spleen (with possible tuberculous involvement of the adrenals). The roentgen-ray department reported large calcified areas in the spleen and indicated that the findings (see figure 7) were compatible with the diagnosis of primary tuberculosis of the spleen.[22, 23, 24] The patient was afebrile. The human tuberculin skin test was negative, but the bovine tuberculin skin test was strongly positive which again was compatible with the suspected diagnosis.[23, 25, 26] Greppi [27] and Fox [28] believe that active primary tuberculosis of the spleen is associated with anemia, the chronic form is associated with polycythemia. Wintrobe [29] states that "about 82 cases (tuberculous splenomegaly) have been reported" by 1942 and also points out that tuberculous processes in the spleens of patients with polycythemia (he has had two cases) are not uncommon.

Gastric hemorrhages in primary tuberculosis of spleen are not unusual,[22, 30, 31, 32, 35] and because of the positive bovine tuberculin test, the roentgenological findings, the persistently low hemoglobin and white blood cell levels, but high red blood cell levels, which were unaltered by iron therapy, the attacks of syncope and the patient's intense fear of additional gastric hemorrhages, splenectomy was agreed upon. Upon opening the abdomen diffuse chronic adhesive peritonitis was strikingly evident, gall stones could be palpated, but the liver grossly revealed no cirrhosis and the spleen was firmly matted with dense adhesions to almost all of the structures located in the area of the upper left quadrant. The veins between the spleen and stomach were unusually large and abnormally abundant. The portal veins and splenic vein could not be thoroughly examined. During the operation 3,000 c.c. of

blood, 3,000 c.c. of saline and 80 grams of dried plasma restored in 250 c.c. of distilled water were necessarily administered. The spleen weighed 1,020 grams and contained, in addition to others, two large (2 by 3 by 1 cm.) calcified plaques about the large veins at the hilum. Pieces of the spleen were emulsified and injected into guinea pigs; other pieces were dried. Several pieces from several sections of the spleen were fixed for microscopic examination. The patient died the third postoperative day (extensive pulmonary edema) and every effort to obtain an autopsy failed.

The microscopic findings of the spleen were unusual in that the typical features of the Banti's syndrome (fibrosis, marked hyperplasia of the reticular cell system, hyaline degeneration of the pulp, etc.) were observed but there was no pathological evidence of tuberculosis; and the typical findings of polycythemia (hypertrophy of pulp, marked congestion with red blood cells, hematopoiesis, etc.) were absent. Weber [33] states that the Banti's syndrome may occasionally be associated with an erythrocyte count above normal (anemia splenica sine anemia) but does not present a case and we have not been able to find an authentic case reported in the literature. Weber speaks of "erythrocytosis secondary to blood stasis" (thrombosis of portal vein, splenic vein, etc.) but Oppenheimer [34] believes that the polycythemia in such cases is primary and the thromboses secondary. It would be difficult to conclude definitely from the pathological evidences found in the spleen, whether the spleen could be classified as one belonging to the Banti's syndrome or as one of long standing polycythemia in which fibrosis and hypertrophy of the reticular cell system were the prominent features. The clinical and pathological evidence together would make one lean towards the diagnosis of the Banti's syndrome.

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THE TREATMENT OF MENINGOCOCCUS CARRIERS WITH SULFADIAZINE*

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THIS paper deals with an investigation of the efficacy of sulfadiazine in clearing the nasopharynx of meningococci. Since the meningococcus carrier is generally considered to be the paramount factor in the spread of an epidemic of meningococcal meningitis, any therapeutic agent consistently successful in eliminating the specific organism from the posterior nasopharynx might well prove to be of considerable value in the prophylaxis of the disease. Various members of the sulfonamide group of drugs have given promising results. The original observations of Meehan and Merrilles [1] on the successful use of sulfapyridine have been confirmed by others [2, 3] and extended to include sulfanilamide [4] and sulfathiazole as well.[5] For the present study sulfadiazine was the drug of choice because of its low toxicity and the excellent therapeutic response obtained with it in the treatment of clinical cases. A control group of untreated carriers was included so that the specific action of the drug might be truly evaluated.

TABLE I

Results of Nasopharyngeal Cultures on a Sample of the Camp's Population

Total Number Cultured	Type I		Type II		Type II Alpha		Untypable Meningococci		Total Carriers	
	Number	%	Number	%	Number	%	Number	%	Number	%
1004	469	46.7	55	5.5	39	3.9	16	1.6	579	57.7

During the winter of 1942–1943 an outbreak of meningococcal infections occurred in a large naval construction training center. Cases of both meningitis and uncomplicated septicemia were observed; in over 90 per cent of these a Type I meningococcus proved to be the causative organism. The response to sulfadiazine therapy was gratifying in that the mortality rate re-

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mained in the neighborhood of 5 per cent. The clinical features of the epidemic are to be reported elsewhere.

A carrier rate determination on a representative sample of the camp's population gave a total incidence of 57.6 per cent, with Type I nearly five times as prevalent as all other meningococci combined (table 1).

The nasopharyngeal cultures were obtained by means of a straight swab and tongue depressor. If they could be brought to the laboratory within two hours the swabs were placed in individual tubes containing 0.5 c.c. of Mueller's starch casein-hydrolysate medium [6] made up in fluid form without agar.* Swabs that had to stand overnight were placed in 0.5 c.c. of sterile horse blood in accordance with Mueller's modification of his own method [7] for

TABLE II

Treated Group:

Type	Initial: 0 Hours		72 Hours		144 Hours	
	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
Type I	140	68.96	0	00.00	0	00.00
Other Meningococci	21	10.35	0	00.00	1	00.49
Total Carriers	161	79.31	0	00.00	1	00.49
Negative Cultures	42	20.69	203	100.00	202	99.51
Total Cases	203	100.00	203	100.00	203	100.00

TABLE III

Untreated Group:

Type	Initial: 0 Hours		72 Hours		144 Hours	
	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
Type I	101	54.30	135	72.58	123	66.13
Other Meningococci	7	3.76	15	8.06	19	10.22
Total Carriers	108	58.06	150	80.64	142	76.35
Negative Cultures	78	41.94	36	19.36	44	23.65
Total Cases	186	100.00	186	100.00	186	100.00

preserving gonococcal cultures. The starch casein hydrolysate medium * was used for plating; the Petri dishes were then incubated for 16 hours in a candle jar containing a small amount of thoroughly moistened cotton to insure a properly humid atmosphere. After suspicious colonies had been isolated the organisms were typed by the tube agglutination method; those reacting with polyvalent serum alone were run through sugars before being classed as "untypable meningococci."

Men from a barrack known to have a high carrier rate were divided into two approximately equal groups. These individuals lived, worked and

*Each liter of this medium contains 50 mg. of para amino benzoic acid.

TABLE IV

Treated Group:

Type	Initial: 0 Hours		72 Hours		144 Hours	
	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
Type I	140	68.96	0	00.00	0	00.00
Type I becoming other types, or untypable meningococci	0	00.00	0	00.00	1	00.49
Type I becoming negative	0	00.00	140	68.96	139	68.47
Total	140	68.96	140	68.96	140	68.96
Meningococci other than Type I	21	10.35	0	00.00	0	00.00
Meningococci other than Type I becoming Type I	0	00.00	0	00.00	0	00.00
Meningococci other than Type I becoming negative	0	00.00	21	10.35	21	10.35
Total	21	10.35	21	10.35	21	10.35
Negative	42	20.69	42	20.69	42	20.69
Negative becoming Type I	0	00.00	0	00.00	0	00.00
Negative becoming meningococci other than Type I	0	00.00	0	00.00	0	00.00
Total	42	20.69	42	20.69	42	20.69
Grand Total	203	100.00	203	100.00	203	100.00

TABLE V

Untreated Group:

Type	Initial: 0 Hours		72 Hours		144 Hours	
	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
Type I	101	54.30	95	51.08	75	40.32
Type I becoming other types or untypable meningococci	0	00.00	2	1.07	3	1.61
Type I becoming negative	0	00.00	4	2.15	23	12.37
Total	101	54.30	101	54.30	101	54.30
Meningococci other than Type I	7	3.76	2	1.07	2	1.07
Meningococci other than Type I becoming Type I	0	00.00	1	0.54	1	0.54
Meningococci other than Type I becoming negative	0	00.00	4	2.15	4	2.15
Total	7	3.76	7	3.76	7	3.76
Negative	78	41.94	28	15.05	17	9.14
Negative becoming Type I	0	00.00	39	20.97	47	25.27
Negative becoming meningococci other than Type I	0	00.00	11	5.92	14	7.53
Total	78	41.94	78	41.94	78	41.94
Grand Total	186	100.00	186	100.00	186	100.00

messed together, and, as far as could be ascertained, were equally exposed to other carriers in the camp. On the first day nasopharyngeal cultures were taken on all men; those in the first group were then given three grams of sulfadiazine in divided doses on the first day and similarly three grams on the second and two grams on the third day, each man thus receiving a total of eight grams over the course of 72 hours. The second group, serving as a control, was left untreated. On the fourth day both groups were recultured and urine specimens obtained from those men who had received the drug. No further medication was given, but on the seventh day another nasopharyngeal culture was taken on each man.

TABLE VI

Treated Group:

At 0 Hour: (Start of Experiment)

Type I (A)		Other Meningococci (B)		Negative (C)		Total	
No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
140	68.96	21	10.35	42	20.69	203	100.00

At 72 Hours:

	Type I		Other Meningococci		Negative		Total	
	No.	%	No.	%	No.	%	No.	%
Type I (A)	0	00.00	0	00.00	140	68.96	140	68.96
Other Meningococci (B)	0	00.00	0	00.00	21	10.35	21	10.35
Negative (C)	0	00.00	0	00.00	42	20.69	42	20.69
Total	0	00.00	0	00.00	203	100.00	203	100.00

At 144 Hours:

	Type I		Other Meningococci		Negative		Total	
	No.	%	No.	%	No.	%	No.	%
Type I (A)	0	00.00	1	00.49	139	68.47	140	68.96
Other Meningococci (B)	0	00.00	0	00.00	21	10.35	21	10.35
Negative (C)	0	00.00	0	00.00	42	20.69	42	20.69
Total	0	00.00	1	00.49	202	99.51	203	100.00

No loss in sense of well being was noted in any of the men given sulfadiazine; no rashes occurred; and microscopic examination of the urine obtained from each individual 12 hours after withdrawal of the drug showed no evidence of hematuria or crystalluria. Unfortunately, facilities for determining sulfadiazine blood levels were wanting.

The results are given in tables 2, 3, 4, 5, 6, and 7.

TABLE VII

Untreated Group:

At 0 Hours: (Start of Experiment)

Type I (A)		Other Meningococci (B)		Negative (C)		Total	
No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases	No. of Cases	% of Total Cases
101	54.30	7	3.76	78	41.94	186	100.00

At 72 Hours:

	Type I		Other Meningococci		Negative		Total	
	No.	%	No.	%	No.	%	No.	%
Type I (A)	95	51.08	2	1.07	4	2.15	101	54.30
Other Meningococci (B)	1	0.54	2	1.07	4	2.15	7	3.76
Negative (C)	39	20.96	11	5.92	28	15.06	78	41.94
Total	135	72.58	15	8.06	36	19.36	186	100.00

At 144 Hours:

	Type I		Other Meningococci		Negative		Total	
	No.	%	No.	%	No.	%	No.	%
Type I (A)	75	40.32	3	1.61	23	12.47	101	54.30
Other Meningococci (B)	1	0.54	2	1.07	4	2.15	7	3.76
Negative (C)	47	25.27	14	7.54	17	9.13	78	41.94
Total	123	66.13	19	10.22	44	23.75	186	100.00

All of 161 carriers given 8 grams of sulfadiazine over a period of 72 hours had become negative by the fourth day. After an additional three days during which they received no further treatment, 160 or 99.51 per cent remained negative. The one case which became positive showed a change in type (Type I to Type II alpha) suggesting that it was a new infection rather than a recrudescence of an old one. The control group receiving no treatment during the same period showed a statistically significant increase in the total carrier rate during the first 72 hours, and during the second 72 hours a slight decrease which, however, was not statistically significant. The results may be summarized in table 8.

Ninety men from the company receiving sulfadiazine were subjected to nasopharyngeal cultures on the nineteenth day after the drug had been withdrawn, and a carrier rate of 15.5 per cent was obtained. This process was repeated on the thirty-seventh day and in addition cultures were obtained from 134 men of the control company which had received no specific chemotherapy. During this period both groups had been carrying on their usual duties in camp and had continued to share the same barracks. Among the controls, meningococci were isolated from 81.3 per cent of the cases;

TABLE VIII

Percentage of Total Cultures Positive

Group	Total Population	0 Hours	72 Hours	144 Hours
Treated	203	79.31	00.00	00.49
Untreated	186	58.06	80.64	76.35

The Treated Group: 8 grams of sulfadiazine per man in the first 72 hours.
The Untreated Group: No specific chemotherapy.
Criterion of Significance: 3 times sigma.

TABLE IX

Results of Nasopharyngeal Cultures on a Sample of the Camp's Population 37 Days after the Close of the Experiment

Group	Day Cultured	Number Cultured	Type I		Other Meningococci		Total Carriers		Standard Error
			Number	%	Number	%	Number	%	
Treated	37	90	18	20.0	0	0.0	18	20.0	4.1
Untreated	37	134	93	69.4	16	11.9	109	81.3	3.3

Criterion of Significance: 3 times sigma.

among the men previously treated, however, the carrier rate had risen to but 20.0 per cent (table 9). Carriers successfully treated with sulfadiazine became reinfected relatively slowly after the withdrawal of the drug in spite of constant exposure to the specific organism.

DISCUSSION

Sulfadiazine is apparently fully as effective as other members of the sulfonamide group in the treatment of meningococcus carriers. No positive cultures were obtained after a course of 8 grams administered over a period of 72 hours. Although there was no evidence of drug toxicity among the men treated, a smaller dose would be preferable if it were equally effective. That such may be the case is suggested by the observation that of 12 carriers given 4 grams of sulfadiazine in divided doses during 12 hours, all 12 yielded negative cultures 24 hours later. This question should be subjected to further investigation under controlled conditions.

Some possible practical applications of these results are obvious. If the entire population of the camp was treated simultaneously most, if not all, of the carriers should become negative within 72 hours, and the further spread of the epidemic halted. Emphasis must be laid upon "simultaneous treatment" since our limited experience leads us to believe that a fair proportion of former carriers cleared up by means of specific chemotherapy tends to become positive once more during the ensuing weeks if they are continually exposed to reinfection.

Mass therapy in this manner might not always be practicable because of the amount of drug required and because of the minute but ever present

danger of drug reactions. Smaller groups of men about to leave the camp for duty elsewhere might well be subjected to such a course of chemotherapy for the twofold purpose of diminishing the chances of clinical cases occurring subsequent to their departure, and of insuring the prevention of the spread of the disease to fresh bodies of men by means of carriers.

As shown in tables 5 and 7, the carrier rate among untreated individuals varied considerably on three successive nasopharyngeal cultures taken 72 hours apart. Only 94 (or 50.5 per cent) gave consistent results throughout, the others showing one or more changes in type, or from positive to negative, or vice versa. One individual showed a Type II alpha on the first examination, a Type I on the second, and a Type II on the third. Although every effort was made to use standard methods of culture, isolation and typing throughout the three examinations, it is impossible to say that the variations noted were due entirely to true biological changes rather that to unavoidable differences in technic. Our experience bears out Branham's view [8] that a more accurate picture of the carrier state is given by several examinations of the same sample as compared to a larger group cultured but once.

Summary

Sulfadiazine is effective in clearing the nasopharynx of meningococci since all of 161 meningococcus carriers receiving 8 grams of the drug over a period of 72 hours yielded negative cultures on the fourth day. No untoward effects from the drug were noted and men so treated reacquired latent infection but slowly, in spite of constant exposure to the specific organism. Some possible practical applications of these facts are discussed.

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HEPATIC DAMAGE ASSOCIATED WITH SULFONAMIDE THERAPY IN INFANTS AND CHILDREN. I. MORPHOLOGIC PATHOLOGY *

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THE introduction of the sulfonamides into chemotherapy undoubtedly has reduced appreciably the mortality rate of many infections. However, certain untoward effects were not unexpected because of the inherent toxicity of these drugs and because of individual idiosyncrasy. A number of clinical reports have appeared regarding the deleterious effects of the sulfonamides on the hematopoietic system and the urinary tract. Toxic effects on the liver, as indicated by the development of jaundice, have been of less frequent occurrence. Varying degrees of pathologic change have been found by us in the liver of several infants and children dying during the course of sulfonamide therapy, although during life there was little evidence of jaundice. This paper deals with the liver pathologic lesions encountered.

The first recorded case of hepatic damage associated with the sulfonamides was reported in 1937 by Hagerman and Blake [1] who in discussing febrile reactions with sulfanilamide therapy cite one instance of jaundice which cleared up on discontinuance of the drug. During the following two years seven other investigators [2, 3, 4, 5, 6, 7, 8] listed 11 patients showing injurious effects on the liver from sulfonamides. Four of these patients died and in the only one in which necropsy was performed, Cline [6] found acute yellow atrophy. In 1941, Berger and Applebaum [9] observed early acute yellow atrophy following ingestion of 26.6 gm. of sulfanilamide. About the same time Tragerman and Goto [10] found both clinical and histologic evidence of liver and kidney damage in a patient in whom death had followed the administration over five days of 34 gm. of sulfanilamide for gonorrheal arthritis. Spring and Bernstein [11] and Rothstein and Cohn [12] have recorded one and two cases respectively of toxic hepatitis following sulfathiazole. Hoyne and Larimore [13] have described cloudy swelling of the myocardium, liver and kidney in a patient who received this drug. Lederer and Rosenblatt's [14] recent observation of focal necrosis in the liver and other organs of four patients following sulfathiazole treatment indicates that widespread pathologic change may be associated with sulfonamide therapy. Their youngest patient was 15 years of age. There have been few reports of liver damage in children associated with the sulfonamides. Carey,[15] commenting on the use of sulfanilamide and related compounds in pediatric practice, says "a few cases of hepatitis and jaundice have been observed during chemo-

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therapy in infants and children." Greiner [16] has noted icterus, enlarged and tender liver, with tyrosin and leucin in the urine, following the administration of sulfapyridine to two children.

Various symptoms associated with sulfonamide therapy have been observed in this hospital. A decrease in the number of circulating leukocytes, reflected in a depression in maturation of the late myelogenous elements of the bone marrow, was most frequently encountered. A moderate number of children have shown hematuria and skin lesions, and occasionally jaundice has occurred. An increased incidence of hepatic lesions in children in whom sulfonamide therapy has been the one common factor has been observed by us in postmortem studies during the past three years. Sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine were included in the therapy. We believe that the pathologic changes in the liver are referable to the sulfonamide used.

During the three years ending April 1, 1942, 299 necropsies were performed in Children's Hospital and among this number 38 cases of definite liver disease were studied. These 38 cases were divided into three groups, depending on the severity of the pathologic changes. The first group included three patients in whom the outstanding lesion was a focal necrosis of the liver. Group II consisted of nine patients in whom definite central necrosis was the most prominent feature. The remaining 26 patients forming group III showed beginning central necrosis on a background of serous hepatitis and hepatic cellular dissociation.

Group I. The three patients comprising group I will be discussed individually. All the pathologic findings will be included, but only the hepatic lesions will be described in detail. Two patients received sulfapyridine and one received sulfathiazole.

Case Reports

Case 1. C. R., a five month old, white male, was admitted to the hospital on February 20, 1939 with fever and convulsions which occurred 12 hours before admission and which had been preceded by a cold for two weeks. Pneumococcic meningitis which had its origin in a right pneumococcic mastoiditis was present.

Physical examination revealed an acutely ill child with a tense and bulging fontanelle. The pupils did not react to light and the right ear drum was dull and bulging. There was a mucopurulent nasal discharge. Moist râles were detectable through the entire chest, but there was no definite evidence of consolidation. Reflexes were normal. Kernig's sign and nuchal rigidity were absent.

Urinalysis showed 1 + albumin with occasional granular casts and white blood cells. The hemoglobin was 8.5 gm., the red blood cells 3,000,000 and the white blood cells 24,000 with 62 per cent polymorphonuclear cells. Roentgenogram of the chest showed small shadows scattered throughout both lobes. Spinal fluid was under pressure and contained 12,000 cells per cu. mm., mostly polymorphonuclears, and pneumococci, type 27. Sulfapyridine was given at three hour intervals for eight days to the amount of 17 gm. The temperature remained between 102° and 104° F. during the first week. On February 22, 1939 a bilateral myringotomy was performed. Spinal fluid on the eighth day contained 600 cells per cu mm. Sulfapyridine was discontinued for 24 hours and the temperature rose promptly to 106° F. Sulfapyridine was again

started; in the next three days 3.5 gm. were given and the temperature fell to 100° F. The spinal fluid became clear and contained only 45 polymorphonuclears per cu. mm. Sulfapyridine was again discontinued. The temperature rose to 106° F. The general condition became poor and, on March 6, 1939 deep jaundice appeared over the entire body. A whole blood transfusion of 75 c.c. was then given. The child had also received pitressin and magnesium sulfate from time to time in an attempt to relieve the abdominal distention. On March 7, 1939 the patient died.

The necropsy was performed five hours after death. The principal gross findings were a pneumococcic meningitis, bronchopneumonia, ascites, jaundice, hepatomegaly and left mastoiditis. The meninges were infiltrated with a thick purulent exudate which covered the base and lateral surfaces of the brain, which was soft and congested. The liver weighed 348 gm. and was of a brownish color, mottled with lighter areas which suggested focal necrosis.

Microscopically, besides necrosis of the liver there were in the other organs focal areas of degeneration with partial loss of myocardium, interstitial pneumonia, acute and early chronic glomerulonephritis, acute splenitis and interacinar fibrosis of pancreas.

Liver. The architectural pattern of the liver was maintained, but histology was interrupted because of necrosis of about 10 or 15 per cent of the liver cells. Throughout there was a serous hepatitis with cellular dissociation, and irregularly distributed central and focal necrosis. The picture varied in intensity in different parts of the liver. The serous hepatitis was characterized by shrinking of the liver cords with widened perisinusoidal (Disse) spaces. The cytoplasm was dense except where hydropic, fatty or granular degeneration had occurred. The Disse spaces contained a variable amount of pink granular material and an occasional red blood cell and were intersected by a loose reticular network of fine, wrinkled fibrils extending between the Kupffer and hepatic cells. The endothelial cells were somewhat hypertrophied in the vicinity of their nuclei. The sinusoids contained serum and blood cells and a moderate number of polymorphonuclear cells. Areas of beginning central necrosis showed fatty infiltration and fatty or granular degeneration progressing to necrosis and loss of cytoplasm. The majority of the nuclei took a fairly normal stain but a small percentage was pyknotic or had disappeared. There was an extensive bile stasis and many of the canaliculi were ruptured. In addition there were small patches of focal necrosis, four to six liver cords in diameter, showing cells either shrunken and deeply stained, or undergoing dissolution and having a vacuolated necrotic appearance (figure 1). Karyolysis or complete loss of nuclei was the rule in such patches. Sometimes the necrotic cells remained as masses of granular debris surrounded by a wrinkled cell membrane. There were in these focal areas many polymorphonuclear cells which sometimes appeared actually to lie within the necrotic cells. Sudan IV staining showed globules of fat in cells throughout the lobule but greatest in number in the areas of degeneration. The necrotic areas were irregular in distribution, but were most frequently seen in the midzone of the lobule. In some parts of the liver there was a coalescence of the necrotic areas with a picture approximating acute yellow atrophy. In the periportal septa the bile ducts frequently contained a pink granular material and an occasional cell. There were few if any inflammatory cells. The wall of the hepatic artery was somewhat thickened. The liver capsule was thin and fairly normal.

Brain. There was an extensive purulent meningitis with edema and degeneration of subjacent cortex. Throughout the cortex, chromatolysis and vascular collaring were seen.

Kidney. Most of the glomeruli were enlarged, but a few were contracted and contained a pinkish homogeneous material in some of the tufts. These small glomeruli, which frequently showed a thickened capsule, were found in cortical streaks

of early scar tissue associated with remnants of degenerating tubules. The vessels in these areas showed a thickened intima. The tubules and especially the proximal convoluted and ascending limb of loop of Henle showed compensatory hypertrophy. Many of the lumina contained pink granular material. There was a considerable loss in the number of collecting tubules and those remaining often contained eosinophilic granular casts.

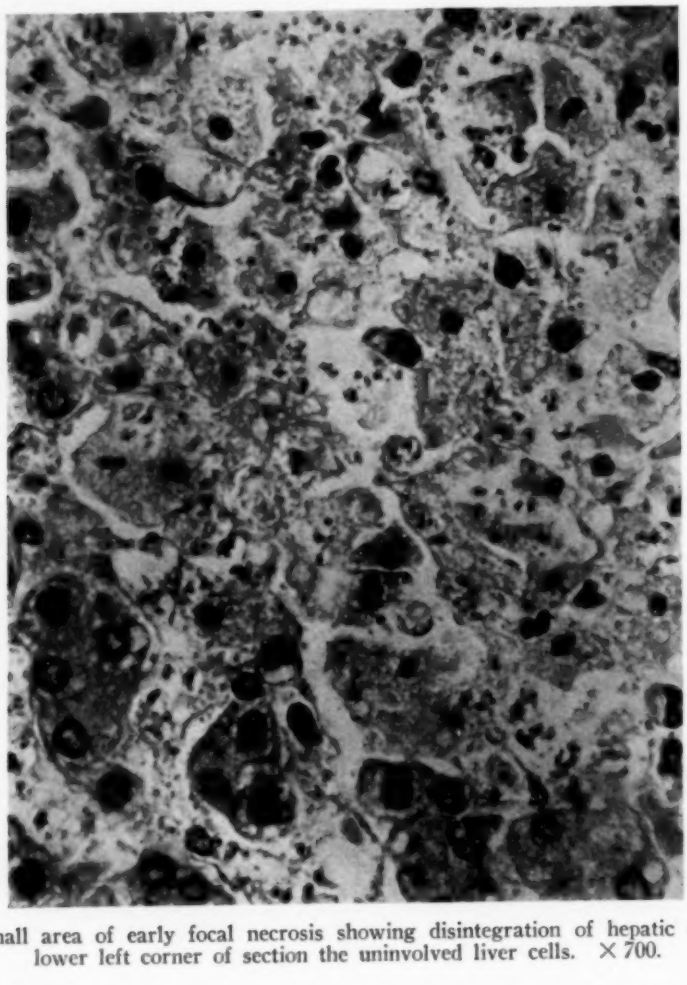

FIG. 1. Small area of early focal necrosis showing disintegration of hepatic cells and at lower left corner of section the uninvolved liver cells. × 700.

Bone Marrow. The bone marrow showed a preponderance of early myeloid cells and a paucity of polymorphonuclears.

Spleen. There was an acute splenitis with marked congestion and pigmentation.

Lung. The lung showed a patchy interstitial pneumonia, most marked around the bronchi in which there was a loss of lining epithelium in part or in whole. The intervening tissue was generally normal. The alveoli in the involved areas contained serum and a few macrophages filled with debris and pigment. The alveolar walls were thickened and contained mononuclear cells. Very few polymorphonuclears were seen in the alveoli or in their walls. No organisms were identified in Brown-Brenn preparations of lung or spleen.

Case 2. P. K. was a well developed, poorly nourished, acutely ill white male child, five months of age, admitted to the hospital on April 3, 1940 with meningitis. The anterior fontanelle was bulging and pulsating. The nasal alae were dilated and the throat was injected. There was a definite nuchal rigidity, reflexes were hyperactive, and the Kernig sign was 1+. The extremities were rigid. There was a slight opisthotonos and a marked tenderness along the spinal column. Physical examination of chest and abdomen was negative. During the child's 39 days of hospitalization his red blood count remained about 3,000,000 per cu. mm., although 250 c.c. of whole blood were transfused over this period. The white blood count varied from 8,600 to 24,500 per cu. mm. Differential count ranged between 74 per cent and 90 per cent neutrophiles. The urinalysis showed a 1+ albumin with an occasional neutrophile. Roentgenogram of mastoid and chest were negative. Spinal fluid on admission showed 3,900 cells per cu. mm., polymorphonuclears predominating, 3+ globulin and pneumococci, type 18.

Sulfapyridine was given by mouth at three hour intervals to the amount of 7.5 gm. for the first four days and then discontinued for one and one-half days. Following this interlude, 36 gm. were given by mouth through the 17 days ending April 25, 1940. At that time only 19 white blood cells per cu. mm. were present in the spinal fluid, but the globulin was still 4+. Culture and smears were negative. On April 19, 1940 the sulfapyridine blood level was too low to be read, and on April 24 was 3.4 mg. per cent. Another 8.5 gm. of sulfapyridine were administered between April 25 and April 30. On the latter date the spinal fluid again contained pneumococci and the cell count began to rise gradually. The dosage was then increased, and 11 gm. were given in the four day period ending May 6 with no improvement. Cells in spinal fluid then reached 1135 per cu. mm. In the next two days, May 6 and 7, in addition to oral administration, 2 gm. of the sodium salt were slowly injected subcutaneously and again on May 9 another 2 gm. of the sodium salt were given subcutaneously, but the child failed to improve. On both May 6 and May 7 the sulfapyridine blood concentration was 3 mg. per cent. Oral administration was continued and in addition on May 11, 4 gm. of the sodium salt were given intravenously. The child died on May 12, 1940, on which day the spinal fluid cell count was 380 per cu. mm. Seventy-four gm. of sulfapyridine had been given between April 3 and May 12. Sulfapyridine blood determinations showed, with the oral administration of sulfapyridine, the highest level was 3.4 mg. per 100 c.c. The level rose to 6.5 mg. after the intravenous administration of sodium sulfapyridine.

The autopsy was performed two hours after death. The chief findings were purulent meningitis and bronchopneumonia. The meninges showed a purulent exudate which was most marked in the frontoparietal regions and along the sagittal sulcus where the meninges were markedly thickened. In the exudate in many of the sulci were small isolated pockets of pus which were being walled by fibrosis. The mastoids and sectioned brain grossly appeared negative.

The liver weighed 292 gm., was slightly enlarged, congested and showed the yellow mottling of central necrosis on a dark red background.

Microscopically, besides the central necrosis, there were acute hepatitis, bronchopneumonia, and acute splenitis. Brain and liver showed the most interesting lesions.

Brain. In addition to a widespread generalized fibrosis of the meninges there were small abscesses situated in the cortical sulci where pus pockets, which had been snared off by fibrin, were being organized. In the cortex there was congestion with chromatolysis and enlarged Virchow-Robin spaces which were filled with many lymphocytes.

Lung. The lung showed an acute bronchiolitis and peribronchiolitis with an encircling patchy interstitial pneumonia. The alveolar walls were thickened because of capillary congestion, neutrophilic and round cell infiltration. Most of the bron-

chioles had lost their epithelium; their walls and lumina were infiltrated with neutrophiles. Many Gram-positive diplococci were seen in Brown-Brenn preparations.

Liver. The liver throughout showed moderate serous hepatitis, cellular dissociation and congestion. The majority of the liver cords were shrunken, the cytoplasm stained a deep pink and showed granular and fatty degeneration. The widened sinusoids contained a fair number of neutrophiles. Many small areas of beginning focal necrosis averaging four or five liver cords in diameter were seen, mostly in the midzone of the lobule. The cells in the center of these areas were shrunken, necrotic and without nuclei. The peripheral cells likewise were undergoing dissolution but the nuclei were pyknotic. Polymorphonuclear cells were beginning to collect at the edges of the foci. In other liver sections the necrotic areas occurred in groups of three or four cells and were much more diffusely distributed. In some parts of the liver coalescent necrotic areas involved at least one-third to one-half of the lobule.

Kidney. Kidneys were similar to those seen in case 1.

Spleen. The spleen showed extensive congestion, intra- and extracellular blood pigment, and very many neutrophiles. The malpighian corpuscles were reduced mainly to the germinal centers, which showed the large constituent mononuclear cells filled with such numbers of degenerating polymorphonuclears as to give the impression of small abscesses. Scattered irregularly throughout the pulp were small necrotic areas, consisting of polymorphonuclears in varying stages of degeneration on a background of large degenerating monocytic cells. We do not believe these areas are comparable to the focal necrosis seen in the liver.

Case 3. The patient, R. S., was a well developed, somewhat emaciated, eight and one-half month old, white male child, acutely ill, semiconscious and cyanotic. He was admitted on January 12, 1941 with a history of fever for 24 hours, cough of two weeks' duration and pneumonia six months previously. The respirations were rapid and there was a flaring of the alae nasi. The nose was full of thick mucus, the tonsils were enlarged, and the pharynx was reddened. There was no nuchal rigidity and the Kernig sign was positive. The mastoids were negative. Over the chest moist crackling râles were heard. Otherwise, the examination was negative except for muscular atonia.

Soon after admission the child had convulsions. The temperature varied between 102° and 106° F. During the 48 hours of hospitalization the child was given at four hour intervals by mouth a total of 8.5 gm. of sulfathiazole, with an initial dose of 0.5 gm.

On admission the hemoglobin was 10.5 gm., red blood cells 4,650,000, the white blood cells 59,800 with 50 per cent polymorphonuclears per cu. mm.

The autopsy, performed one hour after death, showed grossly edema and congestion of the brain, and confluent bronchopneumonia of upper and lower right lobes.

The liver weighed 307 gm. and was approximately normal in size.

Microscopically, the outstanding pathologic changes were limited to the lungs, liver and spleen.

Lung. In the left lung there was an early interstitial pneumonia, bronchiolar in distribution, with thickening of the alveolar walls by infiltrating neutrophiles and mononuclear cells. The alveoli contained mononuclear cells and a few polymorphonuclears.

The right lung showed a confluent bronchopneumonic involvement. The alveolar walls were somewhat thickened with neutrophiles and mononuclear cells. The alveoli contained a pink staining material and great numbers of neutrophiles. In the less involved areas there was an infiltration of monocytes and neutrophiles in the alveolar wall. The epithelium of the bronchi was desquamated and their lumina contained large numbers of polymorphonuclears. The pleura was edematous.

Liver. The general architecture of the liver appeared intact. The cellular structure seemed somewhat loose because of the moderate amount of serous hepatitis, the cellular dissociation, and scattered patches of deep reddish staining focal necrosis. The general cellular pathology was similar to that in case 1 except that there was more hypertrophy of the Kupffer cells and an increased number of round dissociated cells in the liver cords. The sinusoids were somewhat narrow and contained a considerable

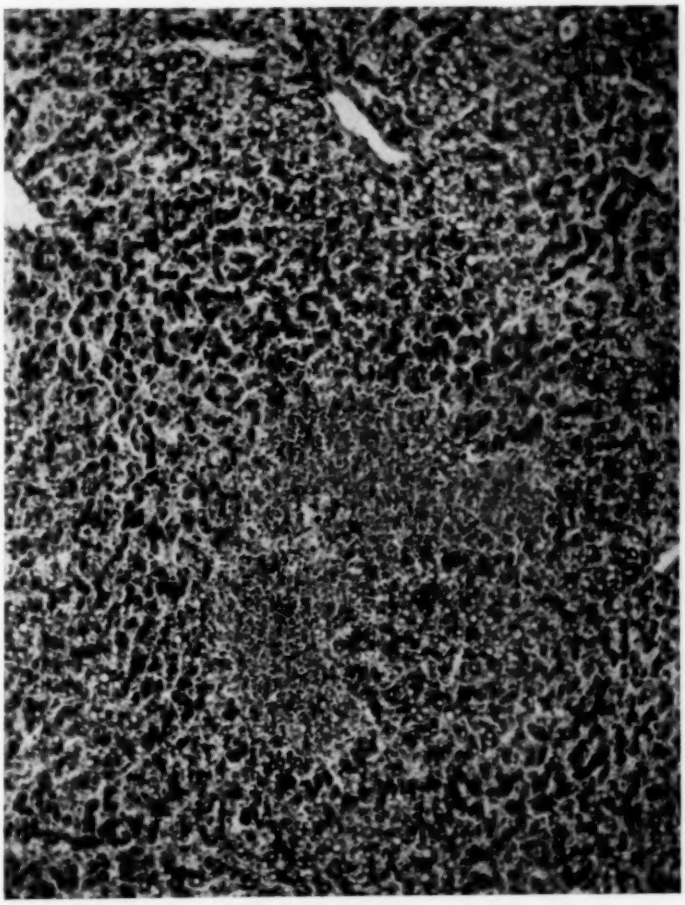

FIG. 2 (A). Section of liver showing area of focal necrosis. × 110.

amount of serous precipitate and occasional polymorphonuclears. The focal necrosis in this liver was the most pronounced of the three cases. The necrotic patches varied in size from a width of four or five to eight or ten liver cords (figures 2 A and 2 B). Their position in the lobule varied considerably and they frequently occurred at one edge of the central vein. The patches were distinguished by a dense eosinophilic staining and considerable shrinkage. Many of the cells were rounded and showed marked decrease in size with disintegration of cytoplasm and a wrinkled cell membrane. Polymorphonuclear cells were numerous in such areas and sometimes appeared to be within the necrotic cells.

Adrenal. In the adrenal the zona fasciculata and glomerulosa showed considerable granular degeneration. No definite areas of focal necrosis were seen.

Heart. The heart showed here and there fragmentation with loss of cross striation and pyknotic nuclei, and irregularly distributed nests in which two or three of the heart cells were completely disintegrated. There were no eosinophiles present and no definite areas in which distinctive focal necrosis with neutrophilic infiltration was seen.

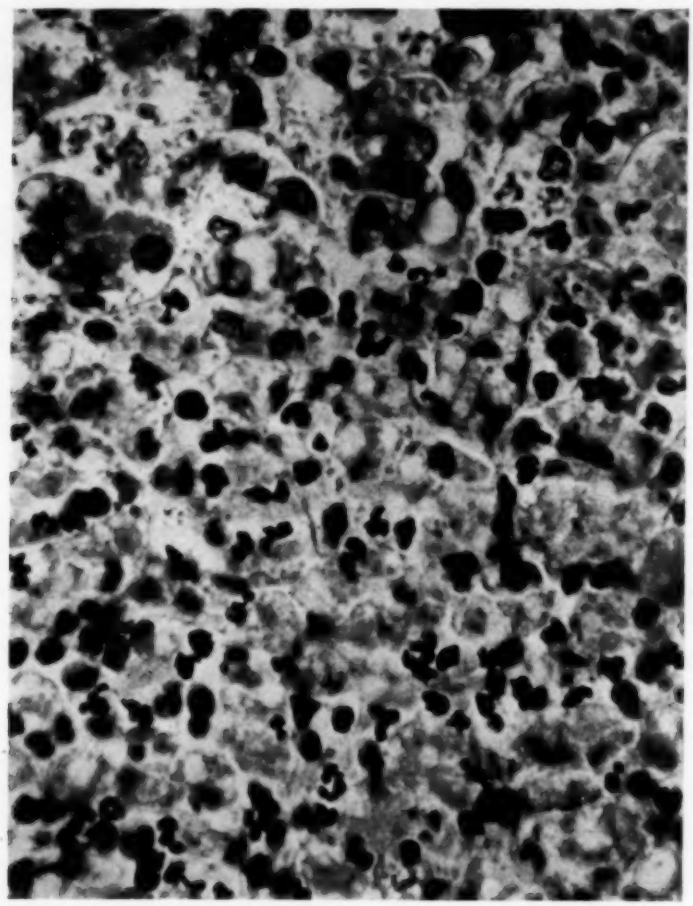

FIG. 2 (B). Showing cellular disintegration and extensive neutrophilic infiltration in the area of focal necrosis. × 700.

Lung. There was a patchy bronchopneumonia in which occurred occasional areas of focal necrosis intersected by the more resistant tissues of the alveolar walls.

Kidney. This kidney resembled the kidney in case 1 except that there was perhaps more tubular degeneration.

Spleen. There was an acute splenitis and a marked thickening of the intimal lining of the capillaries. The malpighian corpuscles were represented mainly by small germinal centers. Small areas of focal necrosis composed of degenerating reticuloendothelial cells infiltrated with neutrophiles were scattered throughout.

TABLE 1

Clinical Diagnosis and Sulfonamide Dosage in Group II Characterized by Central Necrosis of Liver

Name	Color Sex	Age	Clinical Diagnosis	Days in Hospital	Sulfapyridine in gm.	Na Sulfapyridine in gm.	Sulfanilamide in gm.	Sulfathiazole in gm.	Na Sulfathiazole in gm.	By Mouth	Intraspinally	Intravenously	Duration of Therapy in Days	Postmortem Pathology Other Than Liver Lesions
T. C.	W–M	8 mo.	Pneumo. meningitis, type 7	3			2			+			3	Pneumococcic meningitis, type 7, bronchopneumonia, encephalitis, pancarditis, lumbosacral spina bifida
J. M.	W–M	10 yr.	Pneumo. meningitis, type 23	19	35					+			13	Rheumatic pancarditis, pneumococcic meningitis type 23, bilateral bronchopneumonia, chronic gastritis, hemorrhagic colitis, granular degeneration of kidney, generalized bullous dermatitis
D. R.	W–F	9 mo.	Influenzal bronchopneumonia	23		2					+		22	Influenzal meningitis, bronchopneumonia, degeneration of thoracic and spinal cord segments, acute splenitis, granular degeneration of kidney
					33					+				
M. G.	W–F	30 mo.	Influenzal bronchopneumonia	2	4					+			2	Influenzal bronchopneumonia and empyema, acute splenitis, granular degeneration of kidney
R. C.	W–M	9 yr.	Pneumo. meningitis, type 5	1.5		6						+	1.5	Pneumococcic meningitis, type 5, bronchopneumonia, granular degeneration of kidney
					10					+				
D. F.	W–M	7 yr.	Laryngotracheobronchitis	1		1						+	1	Laryngotracheobronchitis (hemolytic streptococcic, group A), acute splenitis, bronchopneumonia
								4.6		+				
P. S.	W–F	10 yr.	Bronchopneumonia	7					19			+	7	Acute splenitis, acute interstitial nephritis, cystic dilatation of pancreas
								7		+				
J. M.	C–F	22 mo.	Pertussis bronchopneumonia	2				1.6		+			2	Umbilical hernia, bronchopneumonia, pertussis
W. E.	W–M	3 mo.	Pneumo. meningitis	1.5		1.6						+	1	Bilateral otitis media, pericardial effusion, ascites, anasarca, dilatation of right heart, pneumococcic meningitis
					2					+				

Comment. The gross appearance of the liver in these three cases gave no inkling of the presence of focal necrosis and the microscopic finding was quite unexpected. This type of lesion had not been observed by us previously in any necropsy material in this hospital and appears to be related to the sulfonamide therapy.

Group II. The characteristic gross picture of central necrosis was seen to a varying extent in all nine livers of group II. In the majority of the livers studied the fine yellow mottling was seen grossly only in the outer half or two-thirds of the right lobe of the liver. This area of the liver has been demonstrated by McIndoe and Counsellor [17] and by Copher and Dick [18] as that receiving blood from the large mesenteric vein, the blood of which maintains its entity as a "stream line" in the portal vein. Thus this part of the liver receives the blood collected from the small intestines which, therefore, contains much of the absorbed orally administered sulfonamides. In three of the cases in which the drug had been injected intravenously late in the treatment, the gross distribution of central necrosis was fairly uniform throughout the liver. Pertinent data relating to the second group have been assembled in the table.

It is of interest to note that pneumococcus, either as a primary or secondary invader was a causative agent. The amount of sulfonamide administered varied widely and bore no definite relation to the extent of the lesion which microscopically ranged from a small area lying immediately around the central vein to the inner two-thirds of the lobule. All of the sections also showed extensive serous hepatitis and more or less dissociation. The dissociated cells varied from those with rounded edges, but still intact and retaining a fair staining quality, to small nests composed of two or three degenerating or necrotic cells with karyolytic nuclei, more or less detached from the contiguous cells of the liver cord.

Group III. The third and largest group of 26 patients showed liver changes consisting of serous hepatitis and a beginning central necrosis. The pathologic change was similar to group II but less in degree and more varied in distribution within different sections. As will be mentioned in the following paper, serum of one of these patients during life gave a positive reaction with the colloidal gold test for liver function. The clinical diagnosis in this group, as in group II, was mainly upper respiratory infections with pneumococci as an outstanding causative agent.

Discussion

A comparison of the recorded number of necropsy cases showing central necrosis during the three years previous to the institution of sulfonamide therapy with the recorded number showing this lesion during a similar period after institution of treatment with these drugs reveals a significant increase under the sulfonamide régime. Only six such cases were encountered in the first triennium as contrasted with 15 cases in the second triennium. The six cases of the first period are made up of two blood dyscrasias with severe

anemia, two encephalitides of long standing, a diabetic coma and an osteomyelitis. The 15 cases, during the sulfonamide treatment period, include two cases of cerebral hemorrhage of the newborn, one granuloma of lung, of unknown origin, one cystic fibrosis of the pancreas with lung abscess, one rheumatic pancarditis, one leukemia and nine cases of infection. In the nine infections, pneumococcus was an outstanding infectious agent. Central necrosis of liver was negligible in these infections in the years previous to drug therapy. The logical conclusion apparently is that the increased incidence of central necrosis of the liver is referable to the added hepatotoxic action of a sulfonamide in the presence of a bacterial toxin. The observed increase in milder hepatic disease accompanying sulfonamide therapy may likewise be explained by this modus operandi. The rôle of serous hepatitis as an initial factor in the development of liver lesions has been stressed by Eppinger.[19] This edematous condition of the liver is not generally of frequent occurrence as Keschner and Klemperer [20] observed only 79 examples, and many of them were in cardiac conditions, in 505 necropsies. Only a small percentage were associated with pneumonias. The possibility that the liver of young individuals may be more vulnerable to toxins than that of adults may explain in part the high incidence of liver injury in our series. With discontinuance of the drug reparation of the damage which occurs in the milder hepatic lesions and restitutions of liver tissue undoubtedly occurs. As stated in the following paper, four cases in which abnormal liver function tests were obtained during treatment were found to be normal three months after the discontinuance of the drug. Presence of retrograde, or regenerated, tissue within the liver may underlie the phenomenon in which a second course of sulfonamide therapy, following a previous course by an interval of a few days to several weeks, leads to more rapidly developing damage than with one continuous series. Other investigators have reported such hypersusceptibility following previous sulfonamide therapy.[21, 22, 23] This type of focal necrosis has not been previously seen by us in children. The histological picture of the focal necrosis produced by sulfathiazole is identical with that described by Lederer and Rosenblatt.[14] A similar pathologic change, although of less intensity, has occurred with sulfapyridine. The development of liver damage is not in direct relation to the amount of drug used and seems to be controlled by individual idiosyncrasy of the patient or some deficiency or alteration in chemical composition of liver. It is not possible at present to say whether this lesion is due to the combined hepatotoxic action of bacterial products and a sulfonamide or only to a specific drug effect. The diversified distribution of the lesion within the lobule supports the latter explanation. Detailed examination of microscopic sections of hearts of children have not revealed the eosinophilic infiltration accompanying sulfonamide therapy described by French and Weller.[24]

Calling attention to the deleterious effect of sulfonamides is not intended to discredit or to discourage their use, but rather to urge the adoption of routine liver function tests as a means of detecting developing liver damage.

Summary

1. In the 299 necropsies performed during three consecutive years in the Children's Hospital of Pittsburgh, 38 instances of liver disease associated with sulfonamide therapy were observed.

2. This pathologic change has been classified as follows. Group I, Toxic necrosis of liver in three patients; Group II, Toxic central necrosis in nine patients; Group III, Serous hepatitis and beginning toxic central necrosis in 26 patients.

3. No definite relationship could be established between the amount of sulfonamide dosage and the development of liver lesions.

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HEPATIC DAMAGE ASSOCIATED WITH SULFONAMIDE THERAPY IN INFANTS AND CHILDREN. II. CHANGES IN LIVER FUNCTION TEST DURING SULFONAMIDE THERAPY *

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SULFONAMIDES have proved effective in the treatment of many infections, and in only a few instances have there been reports of clinical signs of liver dysfunction. This, however, may occasionally occur. The evidence offered in the previous paper of liver disease at times associated with sulfonamide therapy in children led to an investigation of the possibility of the early detection of hepatic damage during treatment. Liver function tests based on alteration of plasma globulin appear to be exceedingly sensitive, and with the use of one of these tests it has been possible to detect changes in liver which occurred during treatment with sulfathiazole or sulfadiazine.

There have been only a few reports in the literature in which liver function has been followed before and during therapy. DeBonis [1] found a decrease in hepatic function in five of 11 normal adults who received 0.03 gr. of sulfanilamide per kilo for three days. Watson and Spink [2] have shown that the administration of sulfanilamide to adults in usual therapeutic amounts causes acceleration of hemoglobin metabolism, and in some of these individuals an elevation of serum bilirubin was noted. Cole and Harned [3] found that the toxicity of sulfapyridine for rats was increased by a vitamin B deficient diet.

METHODS

The functional liver test of Gray [4] was used, which is based upon the fact that colloidal gold is precipitated by the diluted serum from a patient with hepatic disease but not by normal serum. According to Gray this reaction is quite specific for hepatic disease. Eighty-eight out of 96 gave positive reactions, whereas eight gave negative reactions. These eight patients included six with carcinoma of the liver. In addition to being sensitive and reliable if well controlled,[5] this test does not require intravenous injections, solutions by mouth, or the collection of quantitative urine specimens. The original method of dilution was modified so that the test could be made on smaller quantities of serum than previously used. The blood was drawn from a finger puncture by capillarity into a 2 mm. bore glass tube. The opposite end of the tube was sealed in a flame and the tube centrifuged. It was then broken at the line of demarcation of cells and serum, the serum drawn into a 20 cu. mm. hemoglobin pipette and washed into 7 c.c. of 0.9 per cent saline. This gave an initial dilution of 1 to 350, which was further

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diluted to 1 : 3500, 1 : 7000 and 1 : 14000 as described by Gray. Five c.c. of acidified colloidal gold were added to 1 c.c. of each of these three dilutions and the tubes read the next day according to the usual system for the Lange reaction, viz.: red—0, red-blue—1, orchid—2, blue—3, light blue—4, and colorless (complete precipitation)—5. The colloidal gold was freshly prepared every three weeks, the acid requirement determined, and the gold reagent run against a series of negative control sera. The negative sera did not give readings higher than 332. Positive liver damage was indicated by complete precipitation in at least one tube. Some readings fell between the negative and the definitely positive groups and were interpreted as indicating early damage which might have become more marked if therapy had been continued.

The testing of the serum was begun before or during the first few days of therapy at which time the serum gave a negative reaction. The testing was repeated at approximately three day intervals until the determination showed altered liver function or until the drug was discontinued.

Complete blood counts were done on admission and from time to time in order to check any possible deleterious effect of the sulfonamides on the hemopoietic system. Hemoglobin was determined on the Fisher electrohemometer and red cell, white cell and differential counts were made in the usual manner.

The serum concentration of sulfonamides was determined by the method of Bratten and Marshall.[6] Serum levels of drug have not been made routinely in this hospital because it has been found that the levels remain within limits on comparable therapeutic doses and usually do not exceed 7.0 mg. per cent.

Results

One hundred and six patients were tested. Seventy-three of these children with initial negative readings were tested periodically during treatment with sulfathiazole or sulfadiazine. Twenty-four of these patients developed either slight or markedly positive readings in from three to 23 days. These results are tabulated in table 1 together with the type of therapy given. Of the 11 children who gave the more positive findings (table 1, part a) seven had pneumonia whereas the other four had otitis media, diphtheria, tuberculous bronchopneumonia and retropharyngeal abscess respectively. Four of these children returned to the hospital in from two to three months and were retested. It is interesting that all four had negative reactions, thus demonstrating the capacity of the liver to repair. Thirteen patients (table 1, part b) showed slight changes in the colloidal gold reaction. The probability that these changes are indicative of early liver damage is evidenced by the necropsy findings in one fatal case in this group. Death was due to influenzal meningitis and followed 15 days of treatment with sulfadiazine. This patient was included in the previous paper in group III which was characterized by a beginning central necrosis on a background of hepatic cellular

TABLE I

Data on Patients Developing Positive Colloidal Gold Reaction of Serum during Therapy

No. of Patients	Clinical Diagnosis	Age	Sulfadiazine in gr.	Sulfathiazole in gr.	Therapy in Days	Colloidal Gold Reaction	
						Initial	Final
			(*a*)				
7	Broncho-pneumonia	7 Mo.[1]	28		6	332	543
		8 Mo.[1]		40	3	322	532
		7 Mo.[1]	90		8	322	533
		5 Mo.[1]	97		3	322	454
		12 Mo.[1]	160		10	322	522
		6 Mo.[1]	165	168	23	222	554
		4 Yr.	390		6	322	532
1	Acute otitis media	2.5 Yr.	754		23	222	544
1	Diphtheria	11 Yr.	707		10	322	554
1	Tuberculous pneumonia	8 Mo.	243		17	332	533
1	Retropharyn-geal abscess	7 Mo.		92	14	322	542
			(*b*)				
7	Broncho-pneumonia	3–30 Mo.	(5) 67–331		6–11	332–322	422–433
				(2) 111–225	4–7	322	
1	Lobar pneumonia	8 Yr.	450		7	322	432
1	Influenzal meningitis	1 Yr.[2]	1121		15	322	422
1	Scarlet fever	10 Yr.[2]	538		11	322	433
1	Pertussis	30 Mo.	277		11	222	422
1	Pharyngitis	4 Yr.	389		12	322	422
1	Otitis media	10 Mo.	68		3	332	433

[1] Reaction had returned to normal within three months.
[2] Necropsy.

dissociation. It is also significant for the evaluation of this liver function test that the serum from many children passed from a negative test through gradually increasing degrees of positivity to reach a final markedly positive reaction. A concrete case exemplifies this. The initial reaction of the serum

from one child was 222; the reactions in five, 17 and 33 days were 422, 533 and 543 respectively. It would seem that there were progressive changes in the serum globulin which caused progressive increases in the precipitation of the gold reagent.

There were no significant changes in the hemoglobin or in the red cell, white cell and differential counts.

Data on the 49 children who showed no alteration in colloidal gold reaction of serum during therapy are tabulated in table 2. Forty-one of

TABLE II

Cases Showing Normal Colloidal Gold Tests during Treatment with Sulfathiazole and Sulfadiazine

Total No. of Patients	Clinical Diagnosis	Age	No. of Patients	Therapy		
				Sulfadiazine in gr. (Range)	Sulfathiazole in gr. (Range)	Duration in Days
27	Bronchopneumonia	2–24 Mo.	15	75–223		3–9
			7		131–300	3–8
			5	23–148	57–148	7–13
10	Bronchopneumonia Otitis media	4–21 Mo.	9	71–285		
			1		96	4
1	Bronchopneumonia Empyema	9 Mo.	1	55	312	15
4	Tracheobronchitis	9–18 Mo.	3	140–231		4–10
			1		102	3
2	Meningococcic meningitis	5–8 Mo.	2	231–714		7–12
2	Influenzal meningitis	2 Yr.	1	621		42
		3 Mo.[1]	1		113	8
3	Lobar pneumonia	6 Mo.–13 Yr.	3	100–315		7–10

[1] Necropsy.

these patients had pneumonia, four meningitis, and four tracheobronchitis. One child died from influenzal meningitis and necropsy was performed. The changes in the liver were not marked. They consisted of some granular degeneration of the cells and a moderate serous hepatitis. The changes were similar to those found in two cases of influenzal meningitis which had not received sulfonamides before death.

Single determinations were done on a group of positive and negative control sera and on a number of sera obtained from patients with various diseases in order to compare the type of reaction obtained. These have been included in table 3. One child in this group deserves special comment. She

was admitted with a history of anemia of long duration with a decrease in the number of myelogenous cells and a large number of nucleated reds. The tentative diagnosis was lymphatic leukemia. She was given sulfonamides for a throat infection, and the colloidal gold reaction of the serum changed from negative through a slight positive to a marked positive reaction in three weeks. This case was not included in the first table because it was thought that the blood dyscrasia per se might have influenced the colloidal gold reaction. The child died five weeks after admission, and examination of the liver showed a serous hepatitis with a beginning central necrosis, fatty and

TABLE III

Single Determinations on Positive and Negative Controls, and on Miscellaneous Patients

Number	Clinical Diagnosis	Colloidal Gold Reading	Notes
1	Toxic hepatitis	555	Icterus index 25; cholesterol 300 mg. per cent; esters 47 per cent
1	Toxic hepatitis	544	Cholesterol 60 mg. per cent; esters 10 per cent
1	Congenital obstruction of bile ducts	555	Direct van den Bergh; icteric index 75
1	Vitamin K deficiency	555	
1	Congenital syphilis	222	
1	Lymphatic leukemia [1]	543	Liver showed serous hepatitis, mild central necrosis, extramedullary hematopoiesis
1	Nephrosis	333	
1	Biliary cirrhosis [1]	555	Liver showed advanced biliary cirrhosis
25	Negative controls	322, 222	

[1] Necropsy.

granular degeneration and a diffuse infiltration of lymphocytic cells throughout the liver. These lesions were sufficiently extensive to cause alteration in the serum globulin and therefore the markedly positive colloidal gold reaction.

It would have been desirable to test the colloidal gold reaction of blood serum of a larger number of patients who did not receive sulfonamides in order to compare the effect of infection per se on liver function. This type of control patients was not available, however, because of the general use of sulfonamide therapy by the clinicians in the wards.

DISCUSSION

Marked positive tests for altered liver function were obtained in 13 per cent of the children studied. A slightly positive reaction was obtained in an

additional 20 per cent. This latter reaction was interpreted as indicating a mild liver damage. This interpretation was borne out by the necropsy findings in one of these latter cases which showed the basic liver lesion characterizing the third group which has been described in the previous paper.

No correlation could be found between the amount or duration of the therapy and the change in the colloidal gold reaction. One child developed a positive reaction after 28 gr. of sulfadiazine were given over a period of six days whereas another maintained a negative reaction for six weeks during which time 621 gr. of this drug were administered. It would appear that besides the inherent toxicity of the drug, the vulnerability of the liver to a toxin must vary with the individual. It may be significant that the child who developed the positive reaction following only 28 gr. of sulfadiazine had received 48 gr. of sulfathiazole one month before the sulfadiazine was started. Clinical evidence in this hospital substantiates the evidence presented by other investigators that sulfonamides may at times produce a sensitivity so that succeeding small doses given a few days to a few weeks after the initial series will cause toxic symptoms.[7]

Studies on experimental animals have shown that it is difficult to induce necrosis of the liver by toxins unless the chemical composition of the liver has been previously altered. Low carbohydrate and high fat content of the liver, inadequate protein and vitamin B intake have been implicated in the increased vulnerability of the liver to hepatotoxins.[8, 9, 10, 11] If this can be shown to hold true for the sulfonamides, low liver glycogen might be a significant factor in infants and children whose small glycogen stores may be rapidly depleted by lack of food, by increased metabolism associated with fever, or by a combination of these factors. The ketosis, associated with abnormal levulose tolerance curves, which develops frequently during infections of the upper respiratory tract in children,[12] gives evidence for the rapid depletion of available carbohydrate in the younger individuals. It is also apparent that the available protein and vitamin B may be diminished during infections so that their deficiency must likewise be considered. It has been shown that rats are less susceptible to the general toxic effects of sulfanilamide when they have been previously fed on a high protein diet,[13] and another study on rats has shown that the toxicity of sulfapyridine was enhanced by a vitamin B deficient diet.[3]

It would appear desirable to determine the rôle of inadequate nutrition as a factor in the vulnerability of the liver to sulfonamides before finally evaluating the deleterious effects of these drugs.

Summary

1. Gray's colloidal gold test for liver function was run on the sera of 106 patients. The serum of 73 children was tested periodically during sulfonamide therapy and single determinations were run on the remaining 33 patients for purposes of comparison and control.

2. Twenty-four of the 73 children developed positive colloidal gold reaction during therapy; eleven of these showed markedly positive and 13 slightly positive reactions. The sera of 49 children showed no change in reaction during therapy.

3. Changes in liver function reaction could not be directly correlated with the amount or duration of therapy.

4. The type of reaction obtained in four patients is discussed in relation to necropsy findings.

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THE VALUE OF THE EXAMINATION OF GASTRIC CONTENTS FOR TUBERCLE BACILLI *

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THE importance of sputum examination for tubercle bacilli in pulmonary tuberculosis cannot be overemphasized. The finding of tubercle bacilli in the sputum establishes the diagnosis beyond all shadow of doubt. We are convinced of the necessity of gastric lavage for the detection of tubercle bacilli in these cases in which a positive sputum cannot be obtained by the ordinary method.

This method of detecting tubercle bacilli is said to have been described by Meunier [5] in 1898. He showed, in children suffering from pulmonary tuberculosis in whom sputum could not be obtained, that by means of gastric lavage 80 per cent were found to be positive. Armand-Delille and Vibert,[1] in 1927, examined the stomach lavage in 110 children suspected of pulmonary tuberculosis and found 34 positive cases. Clausen,[3] in 1931, examined the material obtained by gastric lavage from 38 adults with pulmonary tuberculosis in whom he had not been able to find tubercle bacilli by the usual method. Twenty were found to be discharging tubercle bacilli. Poulsen,[6] in 1931, claimed that in his series of cases, in spite of negative roentgenograms he was still able to make a diagnosis of pulmonary tuberculosis by demonstrating tubercle bacilli in the gastric contents. He claims the reason for a negative roentgenogram, negative clinical examination and a positive gastric lavage, is that there may be cavities which are so small that they cannot be detected by roentgenograms nor produce clinical symptoms, yet owing to their anatomical placement, are emptying infected material which after being swallowed by the patient can be detected in the stomach contents. Ulmar and Ornstein,[9] in 1933, quite ingeniously showed how tuberculous patients with negative sputa inadvertently swallowed their sputum. Following the injection of iodized poppy-seed oil into the bronchial tree by means of the bronchoscope, a roentgenogram demonstrated the presence of the entire amount of oil in the stomach. The mechanism of bronchial peristalsis accounts for the bronchial contents being raised to the level of the larynx and swallowed without the mechanism of cough. In a series of 287 cases in which there were repeated negative sputum examinations, approximately 20 per cent yielded tubercle bacilli on examination of the gastric contents. Stadnichenko and Cohen,[7] in 1936, in a series of 600 cases reported a positive finding in 30 per cent by means of gastric lavage. In 1938

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Gullbring and Levin [4] demonstrated tubercle bacilli by gastric examination in 34 out of 105 cases.

During the past four years, in a series of 639 cases in whom tubercle bacilli could not be obtained either in preparations stained directly or by concentration methods, 187 patients or 29.2 per cent were found to have a positive sputum by means of gastric lavage. Thirty-two non-tuberculous cases sent mistakenly to the sanatorium were used as controls; none of these cases yielded a positive result. We believe that because of its reliability and definiteness we are justified in its use in any case suspected of pulmonary tuberculosis. Gastric lavage, apart from its diagnostic value, is of therapeutic importance when it is necessary to decide whether active treatment, such as collapse therapy, should be started. This test is helpful also as a prognostic sign to evaluate the effect of pneumothorax treatment and when it should be discontinued. The determination of when to discontinue pneumothorax is always a serious problem even for the most experienced. Gastric lavage should be done before any case of pneumothorax is discontinued. The test is of importance in deciding as to further surgical treatment. It helps to expose simulators, either those who deliberately deny that they have sputum or those who hand in false sputa for examination. The discharge group from a sanatorium is particularly interesting for it presents, so to speak, a special problem. Here is found a group of cases which, owing to their freedom from tubercle bacilli by ordinary examination, their innocent clinical picture and roentgenogram, have been termed arrested cases. It is safe to assume that a fairly good number of these cases show a positive sputum on gastric lavage. We should adhere to the principle that tuberculous lesions of the lung should not be considered healed until tubercle bacilli are repeatedly absent in the gastric contents. This would result in fewer breakdowns and readmissions to sanatoria. Burckhardt [2] invariably gives an unfavorable prognosis in cases in which tubercle bacilli are found in the gastric contents in the presence of a negative sputum unless the gastric examination becomes negative under collapse or other therapy.

The gastric contents are obtained in the early morning before the ingestion of any food in order to avoid dilution by food and gastric secretion. A Levine tube is passed nasally into the stomach, and with a Luer syringe, 30 to 50 c.c. of the concentrated gastric contents are aspirated for examination for tubercle bacilli. It is our opinion that a specimen obtained by this method gives a higher percentage of positive results than diluted contents obtained by the older method. We employ the method as recommended by J. H. Hanks for concentration of the gastric contents.

Technic. The following reagents are used: (1) digestor—1 per cent sodium hydroxide containing 0.2 per cent potassium alum and .002 per cent bromthymol blue; (2) hydrochloric acid approximately 2.5 N. (25 per cent conc. HCl by volume); (3) ferric chloride solution (1 per cent $FeCl_3$ in distilled water). The concentration is carried out by mixing 5 c.c. of the

gastric content with an equal volume of digestor and this is digested in a water bath at 37° C. for 30 minutes with occasional shaking. 2.5 N. HCl is added drop by drop with shaking until the color of the indicator denotes approximate neutrality. Shake for 30 seconds and if flocculation does not occur in less than five minutes, add 0.2 c.c. of ferric chloride solution and shake again. Centrifuge flocculated sample for five minutes at top speed to pack precipitate and discard supernatant fluid. Prepare uniform smears on glass slides, dry in air, fix by heat and stain by Ziehl-Neelsen's method.

This procedure involves the incorporation of alum in the NaOH used for digesting the gastric samples. When the specimen is neutralized the alum flocculates and collects the tubercle bacilli. This method is simple and possesses the following advantages: 1. It reduces centrifugation time to five minutes or, if filtration through paper is desired, dispenses with centrifugation. 2. It permits preparation of uniform slides, facilitating microscopic examination. 3. It collects bacilli more completely so that a unit amount of sediment contains three to seven times more bacilli than can be collected by direct centrifugation of the same sample. Furthermore, the flocculated precipitates do not interfere with cultivation of tubercle bacilli when small numbers are present.

The utmost care in preparation of the gastric tubes is essential in order to prevent false positive reports. Consequently, we have used the following procedure. The tubes are thoroughly washed with hot water and soap, and are then attached to a special water tap and water is run through them for 30 minutes. Next the tubes are boiled for 30 minutes in a weak solution of sodium carbonate, and finally they are placed on ice overnight.

We are in agreement with other workers on this subject that guinea pig inoculation of the gastric contents is a much more delicate test and yields a higher percentage of positive results than does direct microscopy. Stiehm,[8] in 1939, in a series of 50 minimal cases whose sputum was negative, found that 18 per cent were positive on microscopic examination of the gastric contents and 72 per cent positive on guinea pig inoculation. In a series of 60 cases we found that 25 per cent were positive by direct smear of the gastric contents and 65 per cent positive by guinea pig inoculation.

The following table summarizes the results of the examination of gastric contents of patients with pulmonary tuberculosis as reported by different workers:

Author	Date	Cases	Per Cent Positive
Armand-Delille	1927	110	51
Clausen	1931	53	41
Poulsen	1931	15	80
Ulmar-Ornstein	1933	287	20
Stadnichenko-Cohen	1936	600	30
Gullbring-Levin	1937	105	32
Stiehm	1939	50	72

The following case reports illustrate the importance of gastric lavage in diagnosis in some cases of pulmonary tuberculosis which present a minimum of physical signs and roentgenographic findings:

Case Reports

Case 1. G. O., 23 year old married housewife.

Family History: Mother and grandmother had pulmonary tuberculosis.

Past History: Pneumonia at the age of 13. This patient was admitted with a six weeks' history of weakness, fatigue, loss of appetite and loss of 11 pounds in weight, the present weight being 98 pounds. The temperature ranged from 97 to 98.4° F., pulse 70 to 100, respirations 18 to 24. The sputum was persistently negative on direct smear, but on gastric lavage tubercle bacilli were obtained. The urine was normal, and Hinton test was negative; blood picture was normal. Sedimentation rate was 18 D. L. Examination of the chest revealed moderate dullness over the right apex. The left lung was negative.

Case 2. H. R., 26 year old married nurse.

Family History: Two uncles died of pulmonary tuberculosis. Past history was negative. This patient was admitted with a four months' history of weakness and fatigue, weight loss of four pounds, present weight being 93 pounds. The temperature ranged from 97 to 99° F., pulse 80 to 110, respirations 18 to 22. The sputum was negative on direct smear, but tubercle bacilli were obtained in the gastric contents. The urine was normal and Hinton test negative; the blood picture was normal. Sedimentation rate was 11 D. L. Examination of the chest revealed slight dullness over the left apex. The right chest was negative.

Case 3. K. W., 25 year old housewife. Family history and past history were negative. This patient was admitted with a five weeks' history of dry cough, weakness, fatigue, right-sided chest pains, loss of appetite and loss of 14 pounds in weight, present weight being 118 pounds. The temperature ranged from 97 to 98.8° F., pulse 72 to 100, respirations 18 to 20. The sputum was negative on direct smear but gastric contents showed the presence of tubercle bacilli. The urine was normal and Hinton test negative; blood picture was normal; sedimentation rate was 12 D. L. Examination of the chest revealed dullness over the right base, diminished breath sounds, and a few crepitant râles. The left lung was negative.

Case 4. M. M., 19 year old student nurse. Family history: Negative. Past history: Pneumonia three times at ages of 8, 10, and 14. This patient was admitted with a four weeks' history of slight cough, fatigue and weakness. There had been no weight loss, present weight being 198 pounds. The temperature ranged from 97 to 99° F., pulse 80 to 96, respirations 18 to 20. The sputum was negative on direct smear and on microscopic examination of the gastric contents, but guinea pig inoculation of the gastric contents was positive. The urine was normal and Hinton test negative; blood picture was normal; sedimentation rate was 18 D. L. Examination of the chest revealed slight dullness over the right apex. The left chest was negative.

Case 5. E. B., 40 year old painter. Family history: Wife died of pulmonary tuberculosis. Past history was negative. This patient was admitted with a four months' history of cough, slight expectoration, streaking on three occasions, pains in right chest, weakness, fatigue, loss of appetite and loss of 21 pounds in weight, present weight being 133 pounds. The temperature ranged from 97.6 to 99° F., pulse 70 to 94, respirations 18 to 24. The sputum was consistently negative on direct smear, but examination of the gastric contents revealed the presence of tubercle bacilli. The urine was normal and Hinton test negative; the blood picture was normal; and the sedimentation rate was 9 H. L. Examination of the chest revealed moderate dullness over the right mid-lung field with a few medium râles. The left chest was negative.

Case 6. E. M., 25 year old male librarian. Family history and past history were negative. This patient was working and well when he was called to appear for examination at the Army induction center. A routine roentgenogram revealed evidence of pulmonary tuberculosis, and he was advised to enter the Sanatorium. On admission the patient was asymptomatic. Temperature ranged from 97.2 to 98.6° F., pulse 74 to 86, respirations 20 to 24. The sputum was persistently negative on ordinary examination but gastric lavage revealed tubercle bacilli. The urine was normal and Hinton test negative; the blood picture was normal; and the sedimentation rate was 10 H. L. Examination of the chest revealed slight dullness over the left apex with bronchial breathing and fine râles. The right chest was negative.

Summary

1. The importance of gastric lavage for the detection of tubercle bacilli cannot be overestimated.

2. Out of 639 cases with negative sputum, 187 or 29.2 per cent were found to be positive by gastric lavage; 32 non-tuberculous cases employed as controls were all negative.

3. Guinea pig inoculation of the gastric contents definitely gives a higher percentage of positive results than direct microscopy.

4. Gastric lavage is an aid not only in establishing a diagnosis of pulmonary tuberculosis but also in its differential diagnosis, treatment and prognosis. It is in addition an accurate gauge of the infectiousness of a patient and helps to determine his relationship to society.

5. We have attempted to show by case reports the reliability and importance of gastric lavage.

We wish to express our appreciation to the Staff and the Laboratory Department.

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EMBOLISM AND THROMBOSIS OF THE POPLITEAL ARTERY—DIAGNOSIS AND TREATMENT *

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The basis of this report will be the presentation of a series of rather typical cases in which occlusion by embolism or thrombosis of the popliteal artery had taken place. Of the 11 cases presented, eight were from the service of the writer and the remaining three were from those of his colleagues. In these 11 patients obstruction of the popliteal had occurred 14 times.

Thrombosis and embolism of the popliteal artery are among the commoner arterial accidents. McKechnie and Allen,[1] in analyzing 100 cases of arterial obstruction found that the popliteal was embolized and/or thrombosed in 44 per cent and the femoral in 37 per cent of these cases. Embolism occurred more frequently in this series than thrombosis, although once the former takes place both proximal and distal thrombosis soon transpire.

Although the symptom picture which develops when an artery is occluded presents rather constant features, there are several factors which determine the outcome of the accident. These are the location and size of the vessel occluded, the speed with which this is accomplished, the time which elapses between the occlusion and the institution of treatment, and the degree of arteriosclerosis present in the obstructed vessel and its collateral channels. An arteriosclerotic closure of a vessel which develops slowly over a period of years is much less likely to produce a massive loss of tissue than a rapid occlusion by an embolus. In Seifert's experience,[2] sudden obstruction of the popliteal artery resulted in gangrene in about 45 per cent of the cases. Because advanced atheroma is likely to be present in popliteal thrombosis and because this accident often occurs in arteriosclerotics more or less advanced in years, gangrene of some degree occurs in a greater percentage of patients in primary thrombosis than in embolism. It appears, however, that embolism tends toward a more extensive loss of tissue than does thrombosis. It is believed that the vascular spasm which is greatest in embolic obstruction is of even greater immediate danger to the patient than the embolus itself. Thomas Lewis [3] does not concur in this belief, concluding that an embolus is too soft in consistency to produce by its impact so marked an effect on the vessel's caliber, and thus account for the early pain experienced. Seifert,[2] however, observed marked vascular spasm while performing an embolectomy. Gossett, Bertrand and Patel [4] believe that an embolus is fixed by this arterial spasm, its distal progress being thus prevented. The establishment of col-

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lateral circulation must depend upon the ability of vessels to dilate so that their blood carrying capacity is multiplied or indeed upon the opening of channels not in every day use. This dilatation is probably due to the action of a histamine-like metabolite caused by tissue ischemia rather than by the vis-a-tergo of the occluded blood stream alone. It is sometimes almost impossible to decide whether the obstruction is embolic or thrombotic. To attempt so to do is important, however, for emboli may be surgically removed while thrombi do not offer such good operative prognoses.

As stasis follows embolism or thrombosis, a distal as well as a proximal clot quickly forms. It is for this reason that diagnosis must be prompt in order to avoid gross intimal damage and the formation of extensive thromboses which prevent the restoration of circulation even though an embolectomy is later performed. This critical period must not exceed six hours and preferably should not be greater than four hours.

In popliteal obstruction, as in arterial occlusion generally, heart disease and vascular atherosclerosis are basically responsible in about 45 and 30 per cent respectively, of all cases. Hindmarsh and Sandberg [5] found that 77 per cent of 45 patients upon whom embolectomies were performed suffered with heart disease. Mitral stenosis with or without auricular fibrillation, myocardial disease and acute infection of the heart valves are the most frequent causes of intracardial clots. Indeed, in approximately 30 per cent of all cases of mitral stenosis coming to autopsy, cardiac thrombosis has taken place. When cardiac irregularities, particularly auricular fibrillation, are present, embolism is more likely. Myocardial infarction with a resultant mural thrombosis is probably the source of the largest emboli and is not infrequently the forerunner of obstruction of the aorta, femoral or the popliteal arteries at their bifurcations. De Takats [6] wisely warns against indiscriminate digitalization in coronary occlusion as favoring the discharge of large mural thrombi. In subacute bacterial endocarditis emboli are usually so small that they are incapable of obstructing a large vessel since an embolus only ceases forward movement when its diameter exceeds that of a distal vessel or when it impinges on its central bifurcation point. Emboli of medium size are apparently not uncommon, i.e., too small to obstruct the aorta, iliac or femoral, yet too large to pass on into the tibials.

The diagnosis of popliteal embolism ought not to present great difficulties. Early recognition of the existence of an arterial obstruction is highly important. Every obstruction of a larger artery represents an emergency no less urgent than the presence of a gangrenous appendix or a leaking ulcer. Such a patient admitted at midday or midnight requires immediate attention. This is no case in which to await the leisurely arrival of the time for routine round making even though the patient may not seem very ill. Unfortunately, in too many instances hours elapse before hospital physicians and days before community physicians become convinced that this medical condition possesses real emergency characteristics. For well known anatomical reasons

left popliteal embolic obstructions are more frequent than right (McKechnie and Allen 3:2[1]).

Pain caused by spasm and ischemia is not always the first symptom nor is it always very severe. Perhaps in less than 60 per cent of all cases, particularly in thrombosis, is early severe pain experienced. Diagnosis may be

TABLE I

	Sex	Age	Vessel	Time Elapsed	Cardiac Lesion	Original Cause of Occlusion	Result
J. W.	M	41	Rt. Pop.	1½ hours	Mitral stenosis with fibrillation	Embolism	Disch. 45th day
J. W. (2nd admission, 2nd occlusion)	M	41	Rt. Pop.	3 hours	Mitral stenosis with fibrillation	Embolism	Death 5th day
I. B.	F	79	L. Pop.	13½ hours	Arteriosclerosis	Thrombosis	Disch. 90th day
A. W.	F	60	L. Pop. Rt. Pop. Mesenteric	30 days 2¾ hrs.	Mitral stenosis with fibrillation	Embolism	Death 6th day
A. S.	F	47	L. Pop.	10 days	Mitral stenosis with fibrillation	Embolism	Disch. 45th day
W. T.	M	74	L. Pop.	3 days	Arteriosclerotic heart	Thrombosis	Death 7th day
I. G.	M	46	L. Pop.	14 days	Myocardial degeneration	Thrombosis	Disch. 48th day
L. C.	M	56	R. Pop.	30 days	Coronary infarction	Embolism	Disch. 27th day
J. L.	M	73	R. Pop.	7 days	Coronary infarction	Embolism	Disch. 62nd day
H. S.	M	68	R. Pop.	2 weeks	Myocardial degeneration	Thrombosis	Amputation. Disch. 38th day
C. S.	M	65	L. Pop. rt. leg 1 yr. earlier	8 days	Myocardial degeneration. Auricular fibrillation	Embolism	Amputation 11th day. Death 27th day
H. C.	M	49	Rt. Pop.	6–8 hrs.	Coronary occlusion	Embolism	Death 16 hrs. Coronary obstruction

much delayed if one always waits for the appearance of pain. Numbness, paresthesia, pallor and coldness may precede pain, and these in popliteal obstruction may be wholly confined to the toes or foot. Loss of motion with distention of the superficial veins of the limb are early symptoms, the former occurring when ischemia approaches tissue asphyxia. In the absence of instruments of precision, pain, paresthesia and coldness in any portion of the lower extremity with the persistence of a femoral pulsation suggest that the obstruction is in one of three places, i.e., at the point of departure of the pro-

funda femoris from the main trunk, at the bifurcation of the popliteal, in the posterior tibial or in the smaller vessels of the plantar arch. The posterior tibial is obstructed in approximately 10 per cent of cases of arterial occlusion. We have often observed evidences of carelessness in so simple a step as searching for the presence of a femoral pulsation on the affected side. A mid-thigh amputation for the relief of gangrene of a foot would, of course, be futile if the obstruction be at the bifurcation of the aorta. On the other hand, the proximal clot may be so extensive that circulation may be destroyed many centimeters above the site of the original embolism. The oscillometer is of much use in verifying clinical information as to changes in temperature as secured by the palpating hand. The use of the histamine or of the salt solution wheal in the absence of histamine serves to confirm the findings of the oscillometer. The surface temperature apparatus is also highly useful. The elevation and depression of a part by revealing the rapid emptying and filling of vessels serve to indicate the presence of obstruction without definitely locating it. The salient features of the patients comprising this series appear in table 1.

Of the 11 cases in this series, eight were male and three female. The average age was 59. The right popliteal was occluded in seven instances, the left in five, both in one (six occlusions in three patients). In one patient the right popliteal artery was embolized twice. The cause of the obstruction was embolism in eight instances, thrombosis in four. In one patient (C. S.) the right popliteal was embolized and the leg amputated 16 months prior to embolism of the left popliteal. The cardiovascular condition which existed was mitral stenosis with fibrillation in four cases, myocardial disease with fibrillation in one case, arteriosclerosis in three and coronary occlusion in three. Three case histories have been selected to illustrate some of the diagnostic and therapeutic points set down in this paper.

Case Reports

Case 1. A. W., female, aged 60, was admitted to the hospital February 3, 1941 complaining of pain, loss of sensation, and coldness of the left leg.

Four weeks before admission, while recovering from an upper respiratory infection, she suddenly experienced a sharp pain on the inner aspect of the left leg near the knee which was quickly followed by pain in the toes and a feeling of numbness and coldness of the entire foot.

The past medical history revealed that the patient suffered with a phlebitis of the left leg following a nephrectomy at the age of 35. She had had rheumatic fever as a child. For several years she had experienced dyspnea on exertion.

Physical examination disclosed a woman apparently in severe pain with fever and evidences of toxemia. The lungs were clear. The heart was enlarged and was actively fibrillating. The first sound was slapping, but no distinct presystolic murmur could be heard. The left leg below the knee was cold and cyanotic. Neither the left popliteal nor the dorsalis pedis artery could be palpated. Pulsations in both femorals were present. Oscillometric variations below the left knee were absent. Two days after admission the same symptoms occurred in the right leg. A diagnosis of embolism, first of the left and then of the right popliteal artery, was made. The

patient was heparinized, paravertebral block was done, and the Pavex boot was employed one hour twice a day to both legs since the patient's condition did not warrant radical treatment. Acute abdominal pain developed on the fifth day after admission to the hospital and a diagnosis of mesenteric embolism was made. The patient died on the sixth day of her hospital stay.

Autopsy confirmed the presence of an older embolism in the left, and a fresh occlusion of the right popliteal artery. The aorta was patulous. The superior mesenteric was closed by a fresh embolus and gangrene of a loop of bowel with peritonitis was present.

This patient with a bilateral popliteal obstruction illustrates the danger inherent in a delayed diagnosis of vascular occlusion, one of the common causes of death (mesenteric obstruction with peritonitis), and some of the methods of treatment commonly employed.

Case 2. J. W., male, aged 41, was admitted to the Jewish Hospital on December 13, 1940 complaining of a productive cough and fever. His temperature was 102.4° F., pulse 112, respirations 32. While at home after several days of an upper respiratory infection he had experienced a chill, substernal pain and had become very ill. He had had rheumatic fever as a child. Tonsillectomy was performed eight years ago. Physical examination disclosed a consolidation at the right base. Liver dullness extended a finger's breadth below the costal margin. There was a presystolic and systolic murmur present with a thrill best felt over the precordium at the level of the fourth and fifth ribs in the nipple line. After two days of the administration of sulfapyridine the temperature fell to normal and remained so for four days. On December 15 the patient began to fibrillate. On December 19, while asleep, he experienced a sudden, excruciating pain in the right leg (region of the popliteal space). All the signs and symptoms of popliteal obstruction appeared (vide supra).

Within one and a half hours treatment was begun which consisted of paravertebral block (L1–2–3), heparinization, the use of papaverine, the alternating pressure cuff, and the thermostatic cradle. One hundred ninety-five c.c. of heparin were given by vein in the next four days, the clotting time (venous) varying from 15 minutes to one hour. Blocking of the sympathetic roots was performed three times on succeeding days.

Papaverine hydrochloride (gr. ½) was administered mostly intravenously every four hours for a period of three weeks.

For 24 hours no dorsalis pedis pulse could be felt nor were there oscillometric variations below the knee or at the ankle. On December 20, an oscillometric variation of ⅛ was noted at the right ankle. In two days a distinct pulsation could be felt in the dorsalis pedis artery, the leg became warmer and regained its color, and the subjective symptoms of numbness and tingling gradually disappeared. The patient still fibrillating was discharged from the hospital on February 3, 1941.

On November 9, 1941 this patient was readmitted to the hospital after 10 months of comparative comfort at home during which he performed light work in his grocery store. The patient now had a fever of 106° F., pain in the chest, and a return of pain in the right ankle and in the right popliteal space. The previously described symptoms and signs of right popliteal occlusion were again present. Rapid auricular fibrillation was present and the patient was now very critically ill.

A diagnosis of pulmonary infarction with pneumonia and popliteal occlusion with cardiac decompensation was made. Paravertebral block, heparinization, and the use of vasodilators and sulfadiazine were at once instituted. Despite all measures, death occurred on November 13, 1942.

Autopsy disclosed the presence of chronic rheumatic aortic and mitral endocarditis. In the left auricle there was a patch of acute ulcerative endocarditis, three centimeters in diameter, on which there still remained large and small clots which appeared to be the source of the repeated popliteal emboli. There were old and new infarctions of the lungs and spleen. The first popliteal embolus had been organized and endothelialized, the lumen of the vessel at its bifurcation being occluded by a fresh embolus.

In this patient the following interesting points are illustrated: a double obstruction of the right popliteal artery, an unusual source of thrombotic emboli in the presence of the more common one (mitral stenosis with auricular fibrillation), and recovery from an obstruction of the popliteal artery following the use of conservative measures.

Case 3. A. S., aged 47, female, awoke at 4 a.m. on February 5, 1941, complaining of pain, coldness, numbness and loss of motor power in the left leg below the knee. The leg was treated by the application of hot saline packs. There was no relief from the above symptoms. On February 15 she noticed discoloration of a bunion on the inner aspect of the first metatarsal joint. The patient was admitted to the hospital on this day.

On examination the left leg was cold below the knee. The left foot was cyanotic. There was no popliteal or dorsalis pedis pulsation. No oscillometric variations were secured below the knee. There was a presystolic mitral murmur and auricular fibrillation. A diagnosis of embolism of the left popliteal artery was made.

The patient was given papaverine hydrochloride (gr. ½) every fourth hour by mouth for 21 days. The alternating pressure and release cuff was used continuously for 10 days. The remainder of the treatment was symptomatic. The patient was discharged on April 1, 1941, with but a small patch of dry gangrene on the outer aspect of the first toe on the affected foot.

Treatment. The treatment to be employed may be of two types, the conservative and the radical. Some clinicians prefer the immediate surgical approach and when the popliteal or brachial vessels are affected this operation seems not too difficult. There are not a few instances in which the immediate removal of an embolus from the aortic, the popliteal or the brachial has proved most effective. Because the source of arterial embolism is so often the heart and because of the great tendency to recurrence, we are strongly of the opinion that the conservative handling of these cases in comparison with one more radical often offers an equal if not a greater chance of saving the limb of the patient. The aims of the conservative treatment are two: the relief of vascular spasm and the establishment of collateral circulation. To relieve vascular spasm, paravertebral block, papaverine and various physiotherapeutic measures which particularly aim to maintain the temperature of the part are employed. To prevent thrombosis and assist in the establishment of collateral circulation, heparin, the passive vascular exercise machine (Pavex), and the Collins-Wilinsky apparatus are employed.

The first concern of the physician when an embolus lodges is the relief of vascular spasm by blocking the sympathetic roots. This, in the case of popliteal obstruction, should be attempted by injecting the first, second and third lumbar roots. Although in the hospital this procedure is usually

performed by a surgeon familiar with the regional anatomy involved, a physician with but little practice may perform this injection satisfactorily. Paravertebral block should probably be performed daily for four or five days following the lodging of an embolus. It is gratifying after a successful block to note the improvement in color and temperature, and the lessening of pain which result when a spastic vessel segment is thus relaxed. Papaverine hydrochloride should be administered intravenously in one-half to three-quarter grain doses every four hours night and day. Denk,[7] in 1934, reported the recovery of seven out of 10 patients with the use of papaverine alone, and Herman and Reid [8] a perfect record of 10 out of 10 patients by using Pavex alone. Such results are most unusual. The limb is immediately placed beneath a thermostatically controlled cradle with the temperature set at about 98° F. The common metal or wooden cradle with electric bulb suspended from its roof is incapable of providing an evenly regulated temperature. To expose the limb to a high degree of temperature is to accelerate metabolism in an already impoverished tissue. The limb should be encased in a flannel operating room boot and of course pressure points prevented.

The prevention of the formation of proximal clots and perhaps the promotion of the seepage of blood through a partially obstructed channel by heparinization should be attempted early. It has been the custom of the writer to administer at once 5 c.c. (5,000 units) of heparin intravenously in 100 c.c. of salt solution, allowing three to five minutes for its entrance into the vein. The apparatus consists of a ureteral catheter placed within the vein of the non-affected foot. This is connected to the tubing from the container by the insertion in the end of the catheter of an 18 gauge needle. The advantage of an arc of 15 to 20 inches for movement of the limb is obvious, and local irritation and the likelihood of infection at the point of injection are reduced to a minimum. Ten c.c. of heparin are added to 500 c.c. of salt solution and allowed to enter the vein at the rate of 2 to 4 c.c. a minute. Coagulation time, taken twice a day, is maintained at about 20 minutes. Passive vascular exercise is given one-half hour twice a day with the gauge set at plus 40 for pressure and minus 30 for vacuum. The Collins-Wilinsky alternating pressure cuff is applied to the thigh continuously except when passive vascular exercise is being administered. If embolectomy is performed, heparinization is always necessary. The writer is of the opinion that the recent suggestions of some clinicians that coagulation time may be maintained at a satisfactory level by sixth hour injections of 5 c.c. of heparin are not practicable. In his hands the periodic intravenous injection of heparin produced an irregular coagulation time curve.

Summary

1. Eleven cases of popliteal occlusion were presented.
2. Comments on the symptoms as related to diagnosis were made.

3. The necessity of early diagnosis was stressed, it being stated that treatment, whether it be radical or conservative, must be begun within the first six hours if good results are to be expected.

4. The value of a carefully planned conservative routine was pointed out.

5. The technic of heparinization was briefly described.

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CHANGES OF THE WATER TOLERANCE TEST IN HEPATIC DISEASE*

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It has long been recognized that liver diseases are frequently associated with disturbances in water metabolism. Hanot made the well known statement "Il y a un oedème hépatique comme il y a un oedème renal." Gilbert and Lereboullet [1] observed in some cases of liver disease oliguria, "opsiurie hépatique," which in severe cases may lead to anuria. Later, experimental observations, particularly by E. P. Pick and his coworkers,[2] established the important rôle of the liver in water metabolism. Analogous clinical observations have also been made.[3] It seemed that the disturbance of water metabolism would be of diagnostic significance if it could be correlated with the nature and extent of hepatic damage.

Experimental Hepatic Damage

Hepatic damage was produced in dogs by one of us (D. A.) by repeated administration of phosphorus and histamine.[3] In the early stages of in-

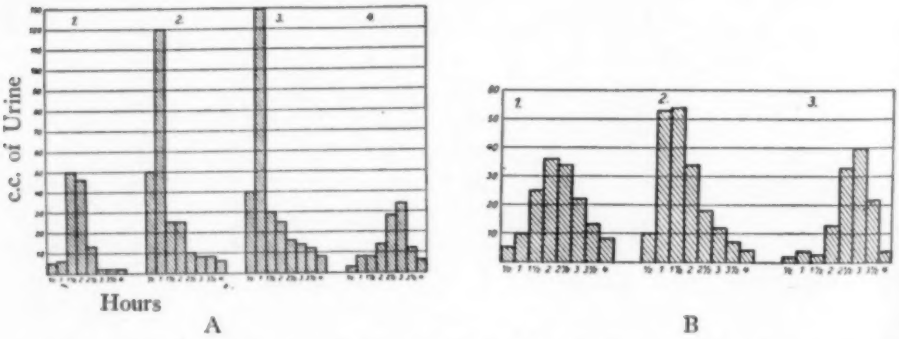

Fig. 1. Progressive changes of the water metabolism in dogs caused by hepatic damage in chronic phosphorus and histamine intoxication.

A. Water tolerance test in experimental phosphorus intoxication.

1. Control after 200 c.c. tap water given by stomach tube to fasting dog (weight 10 kg.)
2. and 3. Examples of early hepatic damage (second week). Exceeding and accelerated diuresis, "shift to the left."
4. Example of later stages (fifth to sixth week). Diminished and delayed diuresis, "shift to the right."

B. Water tolerance test in experimental (chronic) histamine intoxication.

1. Control after 200 c.c. tap water given by stomach tube to fasting dog (weight 6.2 kg.)
2. Example of early stage (first week). Accelerated diuresis, "shift to the left."
3. Example of later stages (third week). Delayed diuresis, "shift to the right."

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toxication, with mild hepatic damage, water intake caused an early and excessive diuresis (figure 1), the curve of which is characterized by a "shift to the left." In later stages with considerable hepatic damage, diuresis was delayed and diminished and showed a "shift to the right" in the diagram. Furthermore, water retention in the tissues was demonstrated by the intradermal wheal test and by chemical determinations.[3]

Clinical Observations

This information was then applied to a clinical study of liver disease. To make the results comparable a uniform technic of performing a water

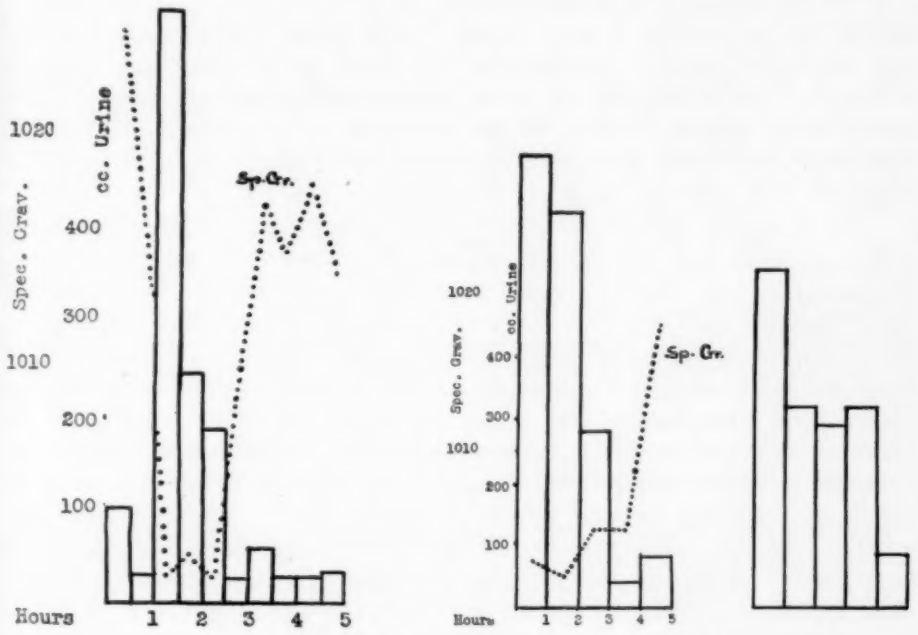

Fig. 2. (*Left*) Normal water tolerance test in man. In this example the total elimination is 1355 c.c. in five hours; rate of diuresis is characterized by maximum output during the second and third hour; spec. gravity (dotted line) varies inversely with water output, the minimum is 1.001.

Fig. 3. (*Right*) Early stage of arsphenamine hepatitis.

A. First water tolerance test (12.4). Total elimination 1780 c.c. Icteric index 60, serum cholesterol 189 mg. per cent.

B. Second water tolerance test, one week later (12.11). Total elimination 1455 c.c. Icteric index rose to 125.

Note early exceeding diuresis in A with marked shift to the left. A week later the shift to the left persists. The findings resemble early experimental hepatitis.

tolerance test was adopted. Fasting subjects were given 1500 c.c. of tap water within 20 to 30 minutes. The bladder was emptied by voiding, and urine specimens were obtained every 30 minutes for five hours. The volume and specific gravity of each specimen were measured and these data were

arranged in a diagram as shown in figure 2, which is representative of the tests performed on 30 healthy control subjects. On this basis, the following criteria of a normal water tolerance test can be formulated. They correspond to similar tests for renal function.[4]

A. Total elimination in five hours: 1200–1500 c.c.
B. Rate of diuresis: The output uniformly rises to a maximum during the second and third hours and then declines.
C. Specific gravity: Fluctuates inversely with the urinary output; the minimum (1.000 to 1.003) coincides with the maximum output during the second and third hours.

The patients with liver disease who were studied, mostly with icterus, may be divided into two general groups: one with parenchymatous liver disease and one without. The diagnosis was established by the usual methods and tests: history and physical examination, roentgenographic examination, icteric index, galactose and sodium benzoate tolerance tests, cholesterol-cholesterol ester ratio, and the d-lactate clearance test. In some cases the diagnosis was verified by aspiration biopsy.

As a result of these many sided investigations it was possible to select a group of patients in whom all the evidence indicated the presence of parenchymatous liver disease (acute and subacute hepatitis). Furthermore, there were included for this study only patients who showed no renal or cardiovascular changes that might influence their water metabolism. In all cases the values of urea nitrogen (or non-protein nitrogen) and of proteins in the blood were normal; the urine was free of albumin and showed the ordinary range of variation in specific gravity. No cases of ascites were included. None of the patients presented signs of the so-called hepatorenal syndrome. In this selected group of patients water tolerance tests were done at intervals. The various stages of their disease were compared with alterations in the water tolerance test in terms of total elimination, rate of diuresis, and fluctuation of specific gravity.

A. Total elimination in five hours. In mild degrees of hepatitis elimination was normal (1200–1500 c.c.) or increased (1800 c.c.). In severe hepatitis the output was diminished (300 c.c. to 1000 c.c.). The retention of water in this test roughly paralleled the severity of the disease.

B. Rate of diuresis. In cases of mild hepatitis the rate of diuresis increased uniformly to the maximum at the second or third hour (as in normals). Not infrequently the rate was accelerated so the maximum occurred in the first hour. When plotted, the peak of diuresis was then shifted to the left. In severe hepatitis this shift to the left frequently appeared at the onset and in later stages was replaced by delayed diuresis, without the usual fluctuations in volume and specific gravity of the specimens. The graphic presentation of the data failed to show the peak at the mid period; in some cases the curve of diuresis was shifted to the right.

C. Specific gravity. In cases of mild hepatitis associated with normal

or increased water elimination, the minimum reached 1.000 to 1.003. In cases of diminished diuresis, the minimum specific gravity, 1.004 to 1.008, was shifted to the left or right and coincided with maximum diuresis.

Parenchymatous Liver Disease. This group comprised 23 patients on the wards of the hospital. A few typical examples are presented below.

Case Reports

C. G., white female, aged 34, was admitted to the hospital following a street accident and transferred to medical wards because of jaundice. The patient was receiving antisyphilitic treatment in the dispensary. The last injection of neoarsphenamine had been given two weeks previously and was followed by a red, itching eruption. The skin and sclerae were slightly icteric, liver and spleen were not palpable. The blood count was normal, the icteric index 60, cholesterol 189 mg. per cent, non-protein nitrogen 25 mg. per cent. Takata-Ara test one week later was moderately positive. Urine contained bilirubin and was otherwise normal. The diagnosis was early arsphenamine hepatitis.

The water tolerance tests performed on admission and one week later are shown diagrammatically in figure 3. The diuresis exceeded the intake in the first test and declined to normal in the second. In both instances the peak of the diuresis occurred in the first hour, resulting in a marked shift to the left of the curve. The specific gravity was similarly shifted to the left. The changes in the water tolerance test in this case of very early acute hepatitis bear a striking resemblance to those in early experimental hepatitis (figure 1).

M. V., white female, aged 57, was admitted with a history of anorexia, malaise and jaundice of two months' duration. The skin and sclerae were icteric. The liver was palpated 2 cm. below the costal margin and later diminished in size and became impalpable. The blood count was normal, the icteric index 23 to 40, cholesterol 312–440 mg. per cent, cholesterol esters 110–150 mg. per cent, Takata-Ara 4 plus, sodium benzoate test positive (less than 0.5 gm.). The urine showed a very faint trace of albumin, bilirubin, and urobilinogen up to 1:160. The diagnosis was toxic hepatitis, possible subacute yellow atrophy.

The water tolerance test (figure 4) showed marked diminution of water elimination; the total output was 384 c.c. The rate of diuresis was characterized by a lack of the normally observed variations resulting in a relatively flat curve. The specific gravity showed markedly impaired dilution.

L. H., white female, aged 48, was admitted because of weakness, moderate weight loss and jaundice of two months' duration. The skin and sclerae were icteric. The liver was markedly enlarged, extending to the umbilicus, and felt firm and nodular. The spleen was also palpable 4 cm. below the costal margin. The blood count was normal, the icteric index ranged from 15 to 40, serum proteins 7.1 per cent, cholesterol 170–460 mg. per cent, cholesterol esters trace to 110 mg. per cent, galactose test was positive (4.2 to 9.0 gm.) on many occasions, sodium benzoate and d-lactate tests were also positive. The urine contained no albumin, urobilinogen up to 1:320 and bilirubin. Aspiration biopsy showed "chronic and acute interstitial hepatitis, liver cell degeneration, striking periportal infiltration with leukocytes." The diagnosis was cholangitic cirrhosis with superimposed hepatitis.

The water tolerance test was followed in this case over a period of four months (figure 5) along with the usual clinical tests. During this time there were fluctuations in the intensity of the disease. The earliest water tolerance test showed a shift to the left. Two weeks later when the jaundice had increased, this shift persisted and the total elimination was diminished. When the icterus decreased five

days later and the galactose test showed improvement, the water tolerance test returned to normal with a normal diuresis pattern. This improvement in the patient's condition was only temporary. Progressive impairment of liver function recurred and was associated with diminished water output and lack of the usual variations in diuresis and specific gravity (hepatitis pattern). Then, two months later, with improvement of liver function, there was also an almost normal water tolerance test pattern.

Similar changes of the water elimination and the diuresis pattern were observed in the next case of arsphenamine hepatitis.

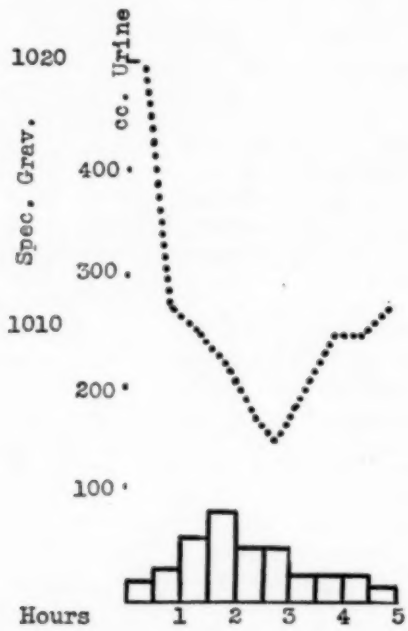

FIG. 4. Typical case of severe hepatitis. Water tolerance test shows total elimination of only 384 c.c., less than half normal; rate of diuresis is abnormal, marked variations of the individual specimens are absent; dilution is impaired, lowest specific gravity is 1.006. Icteric index was 23. Galactose tolerance test and sodium benzoate test were 4 plus positive.

E. V., a Puerto Rican male, aged 30, was admitted with itching and jaundice of two months' duration. The antisyphilitic treatment began 15 months previously and was stopped six months prior to admission because of a generalized eruption. There was intense icterus, the liver was palpable 2 cm. below the costal margin, and the spleen was palpable 8 cm. below the costal margin. The blood count was normal, the serological tests for syphilis were negative, the icteric index was 27, and the cholesterol 165–190 mg. per cent with cholesterol esters 32–80 mg. per cent. The galactose test was positive (6.1–7.1 gm.), sodium benzoate 0.8–2.5 gm. The urine was positive for arsenic, bilirubin, and urobilinogen up to 1:160. The diagnosis was arsenical hepatitis of long duration.

Slow, progressive impairment is indicated in the first three curves by the reduced output and diminished fluctuations of volume and specific gravity (figure 6). There was no shift to the left. Coincidental with clinical improvement there was also improvement of the water tolerance test.

Obstructive Icterus. The second group consisted of 10 cases of obstructive jaundice caused by stone or neoplasm, one case of congenital hemolytic icterus and one case of "Banti's syndrome." In these cases the water tolerance tests were within normal limits. The diuresis pattern in none of the cases resembled that found in hepatitis. As examples, the curves are presented of one case of obstructive jaundice caused by carcinoma of the

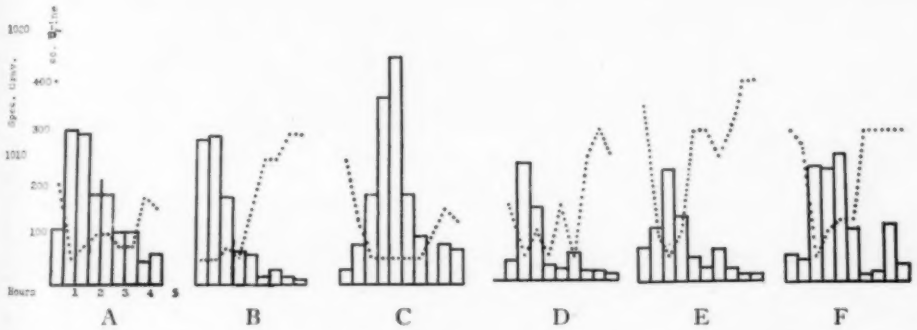

FIG. 5. Changes of the water tolerance test in the course of a long-standing chronic hepatitis.

A. First water tolerance test (10.29). Total elimination 1410 c.c. Icteric index 21, serum cholesterol, 460 mg. per cent, esterified cholesterol 110 mg. per cent. Galactose tolerance test: 8.1 gm. D-Lactate test: 2 plus positive.
B. Second water tolerance test (11.11). Total elimination 947 c.c. Icteric index 40, serum cholesterol 275 mg. per cent, esterified cholesterol 60 mg. per cent. Galactose tolerance test: 5.5 gm.
C. Third water tolerance test (11.18). Total elimination 1544 c.c. Icteric index 18. Galactose tolerance test: 4.2 gm. General condition markedly improved.
D. Fourth water tolerance test (12.6). Total elimination 591 c.c. Clinically, exacerbation of symptoms for past 7–8 days.
E. Fifth water tolerance test (1.28). Total elimination 732 c.c. Icteric index 15, serum cholesterol 170 mg. per cent, esterified cholesterol only in trace. Galactose tolerance test: 9.0 gm. D-Lactate test: 4 plus positive. Patient is gravely ill.
F. Sixth water tolerance test (2.22). Total elimination 1101 c.c. Icteric index 10, serum cholesterol 225 mg. per cent, esterified cholesterol 47 mg. per cent. D-Lactate test: 2 plus positive. Patient is slowly improving.

Note impaired dilution and shift to the left in B with improvement in C, progressive impairment of water tolerance test in D and E coinciding with the clinical picture and then gradual improvement in F.

head of the pancreas, the case of congenital hemolytic icterus, and the case of "Banti's syndrome" (figure 7).

Not infrequently, obstructive jaundice may be associated with hepatic parenchymal damage. These cases present the usual clinical evidence of obstructive icterus whereas laboratory data suggest parenchymal damage. The water tolerance test likewise may show a pattern of hepatitis in these cases. An example of this is shown in figure 8. Initially there was reduced output, delayed diuresis and no marked decrease in specific gravity. The pattern showed marked shift to the right. Later with increasing jaundice, impairment manifested itself by early diuresis with shift to the left. In the last curve, the output was normal but the shift to the left persisted.

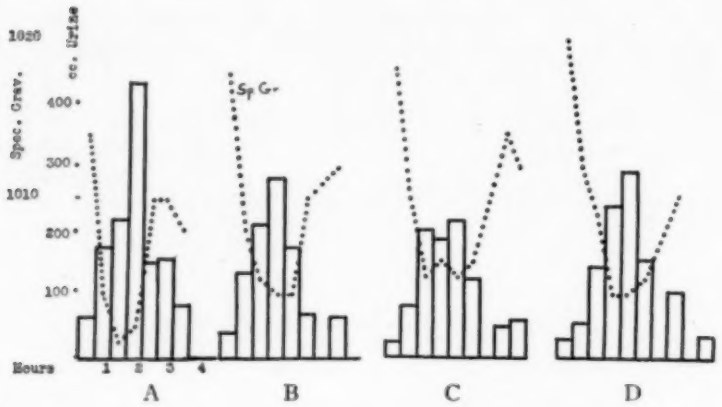

FIG. 6. Progressive impairment followed by gradual improvement in a moderate arsphenamine hepatitis.

A. First water tolerance test (1.23). Total elimination 1292 c.c. Icteric index 27, serum cholesterol 165 mg. per cent, esterified cholesterol 42 mg. per cent. Galactose tolerance test: 7.1 gm. Sodium benzoate test: 0.8 gm.

B. Second water tolerance test (1.28). Total elimination 979 c.c. Icteric index 25, serum cholesterol 175 mg. per cent, esterified cholesterol 30 mg. per cent. Galactose tolerance test: 8.2 gm.

C. Third water tolerance test (2.17). Total elimination 937 c.c. Icteric index 27, serum cholesterol 190 mg. per cent, esterified cholesterol 32 mg. per cent. Galactose tolerance test: 9.1 gm.

D. Fourth water tolerance test (2.25). Total elimination 1051 c.c. Icteric index 20. Sodium benzoate test: 2.5 gm. General condition gradually improving.

Note reduction of total output and impaired dilution, most marked in C, followed by slight improvement in D coinciding with the clinical picture.

DISCUSSION

The observations described above together with the results of the animal experiments [3] confirmed the old clinical impression that parenchymatous hepatic damage is associated with profound changes in water metabolism. This suggests the possibility of using the impairment of water metabolism as a diagnostic sign of disturbed liver function. It is generally acknowledged that impairment of some of the many functions of the liver may occur without changes in the others. This has been shown for experimental hepatic damage caused by phosphorus and carbon tetrachloride [5] as well as in human disease.[6] Accordingly, it was of interest to compare the results of the usual liver function tests with the water tolerance test. Since all of these cases had a galactose test, the following comparison of the 23 cases of hepatitis may be of interest.

Galactose and water tolerance test positive	17 cases
Galactose and water tolerance test negative	2 cases
Galactose test positive and water tolerance test negative	4 cases
Total	23 cases

It is evident that in this small group of cases the simple water tolerance test compares rather favorably with the more elaborate galactose test.

It must be realized that an impaired water tolerance test may be taken as

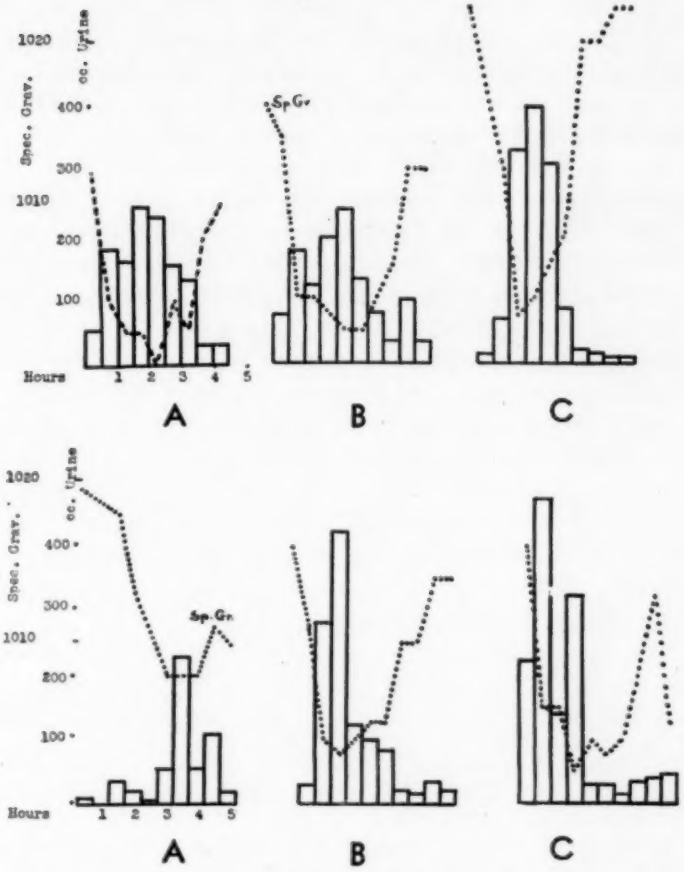

FIG. 7. (*Above*) Other types of icterus and hepatic disease without changes in water tolerance test.

A. Obstructive jaundice, carcinoma of head of the pancreas. Water tolerance test showed total elimination of 1209 c.c. Icteric index 30, serum cholesterol 340 mg. per cent, esterified cholesterol 83 mg. per cent. Galactose tolerance test: 0.8 gm.

B. Congenital hemolytic icterus. Water tolerance test showed total elimination of 1185 c.c. Icteric index 23, serum cholesterol 215 mg. per cent, esterified cholesterol 90 mg. per cent. Galactose tolerance test: 0.5 gm.

C. Hepatosplenomegaly, Banti's syndrome. Water tolerance test showed total elimination of 1268 c.c. Icteric index 6, serum cholesterol 225 mg. per cent, esterified cholesterol 78 mg. per cent. Galactose tolerance test: 3.0 gm. Sodium benzoate test: 2.4 gm.

Note in all three cases: Elimination of water, rate of diuresis and dilution are normal.

FIG. 8. (*Below*) Alteration of the water tolerance test in hepatitis superimposed on common duct neoplasm.

A. First water tolerance test (3.13). Total elimination 538 c.c. Icteric index 23, serum cholesterol 290 mg. per cent, esterified cholesterol 87 mg. per cent. Galactose tolerance test: 5.0 gm. D-Lactate test: 2 plus positive.

B. Second water tolerance test (3.18). Total elimination 1131 c.c. Icteric index 28.

C. Third water tolerance test (3.24). Total elimination 1361 c.c. Icteric index 30, serum cholesterol 320 mg. per cent, esterified cholesterol 145 mg. per cent. Galactose tolerance test: 3.6 gm.

Note in A in addition to reduced output and impaired dilution, the delayed rate of diuresis resulting in a shift to the right; in B water elimination is still impaired although output is increased and dilution better, the rate of diuresis is accelerated causing a shift to the left; in C the output is normal but the shift to the left persists.

an indication of liver damage only when other factors that can affect water elimination are absent. These factors are: hyperpyrexia, cachexia, dehydration, edema, hypoproteinemia, cardiovascular and renal disease, certain endocrinological diseases and hepatorenal syndrome. The presence of ascites obviously precludes the use of the water tolerance test to estimate the hepatic damage in cases of liver cirrhosis. In other words, when any of these conditions are present, the water tolerance test cannot be used as a measure of hepatic damage. This distinct disadvantage is only partially counterbalanced by the simplicity of the test. It can be performed at no cost, without special apparatus at the doctor's office or in the patient's home as well as in a hospital.

The alteration of the water tolerance test in cases of hepatic damage is only one sign of a more profound alteration of water metabolism. Another sign is the not infrequent, latent or manifest edema which may progress to anasarca and ascites at the height of the disease.

Summary

The use of a water tolerance test in liver disease is described. In the absence of other factors influencing water metabolism, a positive water tolerance test is suggestive of hepatic damage.

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ON THE IMPORTANCE OF MALARIA AS A CAUSE OF FALSE POSITIVE SEROLOGIC REACTIONS *

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Stapleton, S. I., N. Y.

The evaluation of positive serologic tests for syphilis is a problem which every physician must face. A diagnosis of syphilis is a serious matter, and its implications may be far reaching. Failure to start treatment in a known syphilitic as early as possible may well be grounds for malpractice. Equally serious and sometimes disastrous is a diagnosis of syphilis in some one who does not have the disease. From a public health point of view this may not be of much concern since in the general population of healthy individuals diagnostic errors due to false positive serologic reactions occur in only about 1 in 4000 individuals.[4]

Looked at from the individual patient's standpoint, however, such statistics mean little. No patient wants to be labeled a syphilitic unless he has the disease since he knows, or soon learns, that this entails prolonged, and unfortunately, in some hands, painful treatment with drugs which are not entirely devoid of danger. Therefore, due caution must be exercised in making every diagnosis of syphilis. In the presence of clinical or historical evidence of the disease the interpretation of positive serologic reactions will in most cases not be difficult. However, when the occasional positive reaction is reported on a patient with no history or physical findings of infection difficulties arise.

In a recent review of this subject Moore et al.[1] have very carefully indicated a method of approach to the problem. They have shown the course of study to which all suspected cases of false positive serologic tests should be subjected.

From numerous studies [1, 2, 3] it has been shown that yaws, leprosy, infectious mononucleosis and malaria are diseases in which positive serologic tests for syphilis can be frequently expected. In occasional instances other conditions, e.g., pneumonia, vaccinia, measles, and other acute febrile diseases may give rise to false positive tests.

Since yaws and leprosy are extremely infrequent diseases in the United States, it will be seen that infectious mononucleosis and malaria will be the chief causes of biologic false positive serologic reactions. Unfortunately both of these diseases are quite common and often are present in a subclinical state.

This is particularly true of chronic or latent malaria. There can be little doubt that when routine blood samples are taken from all personnel of a factory, camp, etc., certain of those taken may be infected with latent malaria.

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This point has been frequently suggested but is difficult to prove. Reports on the occurrence of false positive serologic tests in malaria are all concerned with the occurrence of the positive test in known cases of the disease.[5, 6, 7] That chronic malaria without positive smear will give a positive serologic reaction is still doubted. Mohr, Moore and Eagle state [8] that a positive test may be expected "only during or shortly after the acute febrile illness."

In this paper I shall attempt to show that latent malaria may produce positive tests which may easily be mistaken for latent syphilis and that the distinction between the two conditions will not always be easy. In a review of all the cases of naturally occurring malaria seen at the U. S. Marine Hospital, Norfolk, Virginia, between July, 1936 and July, 1940 the following facts were established:

The total number of cases of malaria was 64.
The total number of cases with positive serologic tests was 19.
The number of cases definitely diagnosed as syphilis was seven.
The number of cases probably due to syphilis was four.

The number of cases with false positive serologic reactions was eight. Of these eight cases in which positive tests were found due to malaria, my attention was immediately called to the following:

Case Reports

Case 1. R. C., a 20 year old white male CCC boy, was admitted to the Venereal Disease Service of the U. S. Marine Hospital, Norfolk, Virginia, on June 25, 1937.

He had been well up to five months before admission when he developed a "sore" on his penis. This had lasted for about two weeks and then subsided and disappeared. Six weeks before admission he had a sore throat and was treated for the "flu." Five days before admission he had "fever" and abdominal pain. One week before admission he had a sample of blood sent to the State Laboratory for routine test along with the remainder of the CCC camp. This blood test was reported positive. A repeat test was sent to the State Laboratory and this was also positive. At the time of admission the patient had no complaints. It was believed on admission that the patient had early latent syphilis.

Physical examination showed some injection of the pharynx and a few small palpable cervical glands. The patient remained well for the next three days. A blood test taken on the Ward on admission showed Kahn reaction was three plus, Wassermann strongly positive. On June 28, 1937 he had a chill and developed a temperature of 40.2° C. A blood smear was taken and showed tertian malaria. This was the first chill the patient had had during his entire present illness. Treatment with quinine was begun.

On 7/1/37	Kahn—3 plus	Wassermann—strongly positive
7/8/37	Kahn—negative	Wassermann—negative
7/12/37	Kahn—negative	Wassermann—negative
7/19/37	Kahn—negative	Wassermann—negative

Prior to the development of the chill this patient was considered definitely syphilitic and would have been treated as such had he not fortunately developed clinical malaria.

A smear had not been taken in this case prior to the chill so that it cannot be stated definitely that he had no evidence of malaria prior to onset of chill. It is my belief that he had chronic malaria, the only manifestations of which were the positive serologic tests.

In the presence of history of penile sore with later developments of a sore throat, with the positive serologic reactions, the diagnosis of syphilis could hardly be criticized.

Case 2. J. W., a 17 year old colored CCC enrollee, was admitted to the hospital July 15, 1939. He had been well up to three days before admission when he developed a headache. He had a moderate epistaxis. Later in the day he had a chilly sensation and several more nose bleeds. During the next two days he had frequent nose bleeds and on the day before admission had another chill. At the time of admission he had no complaints.

There was no history of venereal disease. Physical examination was essentially negative. The temperature was normal on the day of admission with a maximum of 37.3° C. on the following day. The temperature then stayed normal until July 28, 1939. A blood smear was negative for malaria July 19, 1939. On July 17, 1939 Kahn reaction was 2 plus, Wassermann positive. On July 20, 1939 Kahn reaction was three plus, Wassermann positive. A specimen of blood sent to the Venereal Disease Research Laboratory at Stapleton, N. Y. showed Kline exclusion, four plus; Kline diagnostic, three plus; Kahn, negative; Wassermann, positive.

As no evidence of malaria or other acute illness appeared he was transferred to the venereal disease service with a diagnosis of probable early latent syphilis. On July 28, 1939 he had a chill and tertian malarial parasites were found on the smear. Quinine therapy was begun. On July 31, 1939 the following serologic reactions were reported: Kahn, negative; Wassermann, 1 plus, doubtful; Kline exclusion, three plus; Kline diagnostic, one plus. Repeated serologic tests on August 7, August 10, and August 14, 1939, were all negative.

In this case the patient was admitted for malaria, but during two weeks' observation no evidence of malaria or other acute febrile disease was found. Malaria was believed to be ruled out and because of positive serologic reactions he was considered syphilitic. Again, fortunately for the patient, a chill and demonstration of the parasites prevented a long course of antisyphilitic treatment for non-existent syphilis. In these two cases subclinical malaria (a better term than "chronic malaria") gave rise to positive serologic reactions which were assumed to be due to latent syphilis.

It will be seen that errors can be made in the opposite direction, since if it is assumed that all positive serologic reactions obtained during the clinical course of malaria are due to malaria, some cases of latent syphilis will be missed. It is necessary, therefore, that all positive serologic tests found during malarial infection be rechecked until the test is shown to have been falsely positive because of malaria, or else due to syphilis. In this regard the question of how long one can expect the false positive reactions to persist after treatment for malaria has been started will be raised. Kitchen and Kupper [5] found that the seropositive stage varied from eight to 66 days in inoculation malaria, but their patients were of course allowed to have repeated paroxysms and most of the cases were not treated with antimalarial drugs. Nagell and Langhans [8] state that the complement fixation test was

positive in nine out of 10 patients with inoculation malaria. They state that the test again became negative seven to 15 days after the last chill with quinine treatment.

With all the cases seen in this series the serologic reactions became negative within a period of 10 days except for one case.

Case 3. J. C., a 61 year old white male, was admitted to the hospital on November 6, 1939 with a history of chills two days before admission. On the following day he had another chill and blood smear was positive for tertian malaria. Quinine therapy was begun. No further chills occurred. The following is a list of serologic reactions found in this case:

11/8/39	Kahn—4 plus	Eagle—negative
11/9/39	Kahn—4 plus	Eagle—negative
11/11/39	Kahn—4 plus	Eagle—negative
11/13/39	Kahn—4 plus	Eagle—negative
11/16/39	Kahn—3 plus	Eagle—negative

On November 16, 1939 a blood sample was sent to Venereal Disease Research Laboratory at Stapleton, N. Y.

Wassermann—Anticomplementary, Kahn—positive.
Kline Exclusion—4 plus, Kline Diagnostic—4 plus.

11/18/39	Kahn—4 plus	Eagle—negative

On November 18, 1939 a blood sample was sent to Venereal Disease Research Laboratory at Stapleton, N. Y.

Wassermann—Q.N.S., Kahn—doubtful.
Kline Exclusion—4 plus, Kline Diagnostic—doubtful, plus-minus

11/20/39	Kahn—4 plus	Eagle—negative

On November 20, 1939 a blood sample was sent to Venereal Disease Research Laboratory at Stapleton, N. Y.

Wassermann—Anticomplementary; all others, Q.N.S.

11/25/39	Kahn—4 plus	Eagle—negative
11/27/39	Kahn—4 plus	Eagle—negative
12/13/39	Kahn—negative	Eagle—negative
1/12/40	Kahn—negative	Eagle—negative

On January 12, 1940 a blood sample was sent to Venereal Disease Research Laboratory at Stapleton, N. Y.

Kline Exclusion—negative, Kline Diagnostic—negative.
Wassermann—negative, Kahn—negative.

In this case the serologic reactions continued positive for a period of 18 days following the last chill.

It would then appear that if one allows a month to elapse following a malarial infection, the serologic reactions should certainly have become negative, assuming that adequate therapy has been given. In this regard it should be noted that all our cases were treated with the "long course" treatment of

quinine, i.e., daily quinine over a period of six to eight weeks. With the "short course" four day treatment as now advocated by some, the serologic changes to negativity may not be so rapid.

SUMMARY

1. Sixty-four cases of naturally occurring malaria were reviewed.

2. Two cases are cited in which a diagnosis of syphilis was erroneously made on serologic reactions found to be positive because of latent malarial infection. In each case development of clinical malaria occurred before antisyphilitic treatment was begun. It is believed that these two cases will at least partially help to disprove the present accepted belief that the symptomless malarial carrier state cannot produce false positive serologic reactions.

3. The longest period of positivity of serologic reactions with quinine therapy was 18 days after the last chill. This occurred in only one case. The other cases all had negative reactions within a period of 10 days following the last chill.

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THROMBOSIS AND EMBOLISM OF THE ABDOMINAL AORTA *

By Irving Greenfield, M.D., F.A.C.P., *Brooklyn, N. Y.*

Thrombosis of the abdominal aorta was first described by Graham [1] in 1814. In the steadily growing literature, the diagnosis in the vast majority of cases has been confirmed by postmortem examination. The number of reported cases, however, gives a false index of the frequency with which thrombosis and embolism of the abdominal aorta occur. For, as Leriche [2] pointed out, a number of cases are not reported because recovery prevented confirmation of the diagnosis. It is reasonable to state, therefore, that thrombosis and embolism of the abdominal aorta probably occur more frequently than the proved reported cases would seem to indicate.

In 1898, when Welch [3] reviewed the literature, 59 cases were collected. Thrombosis of the abdominal aorta was suspected in 14 of these cases and an embolus in the remainder. Thirty-three additional case reports were added during the next 34 years, and to these Wylde [4] added two cases which he observed, bringing the total number of cases which he reviewed to 94. In an excellent summary of the literature, Banowitch and Ira [5] cited 11 additional cases and added five cases which they observed at the Long Island College Hospital. Rothstein [6] collected and reviewed briefly the reports of 13 cases of thrombosis and embolism of the abdominal aorta which occurred in infants and in children under 15 years of age. To these, his case was added, so that in 1935 the total number of recorded cases was 123. During the past seven years, 33 additional observations have appeared. This brings the total number of cases of thrombosis and embolism of the abdominal aorta reported during the century and a quarter which followed Graham's original description to 156. The purpose of this presentation is to add five additional cases. One of these was observed by the author; and the remaining four † were taken from the records of the Brooklyn Jewish Hospital.

Case Reports

Case 1. A 56 year old white man who had had a right nephrectomy because of tuberculous disease was taken ill with pains in the right upper abdomen several hours after a meal consisting of waffles and butter. The pain was colicky in character, radiated to the right shoulder, and was associated with nausea and general malaise. Four days later a yellowish discoloration of the sclerae and skin was noted. The temperature was elevated to 102° F.; the systolic blood pressure in mm. of mercury was 126 and the diastolic 70. The pulse rate was 84 per min. Bed rest was advised.

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The fever subsided and the icteric tint of the sclerae diminished. At about midnight on the tenth day of his illness, he complained of a "numb feeling" in both lower extremities associated with a desire to urinate. The patient left his bed and 10 minutes later was found lying on the bathroom floor complaining of agonizing pains in the region of the sacrum, the perineum and both lower extremities. He was carried back to bed in shock and was seen within the hour. His lips were pale. The respirations were rapid and shallow. There were frequent cries signifying intense pain. The pulse rate was 110 per min. The blood pressure in mm. of mercury was 120 systolic and 70 diastolic. The only pertinent positive physical finding aside from the lower extremities was a loud harsh systolic apical murmur. The lower limbs were warm but presented a cadaveric pallor. The pulsations of the major vessels of both extremities, though diminished, were present up to the groin. A large dose of pantopon was given to control the severe pain. Because of the diminution of the peripheral pulsations bilaterally together with the intensity and distribution of the pain, a lesion at the bifurcation of the aorta was suspected. The pain was so severe that it was not controlled by pantopon and though the narcotic effect of the opiate was definite, slumber was interrupted by frequent groans which indicated that pain was still present. Within two hours the condition of the extremities had changed. The skin was cool and presented the appearance of cutis marmorata from the groin to the toes. The pulsation of the major vessels of both lower extremities from the dorsalis pedis to the femoral arteries had disappeared. Papaverine was given intravenously without effect. In spite of additional pantopon the patient continued to complain of agonizing pain in the perineum, over the sacrum and in both lower extremities.

On admission to the hospital four hours after the onset of the acute symptoms, the patient was in acute distress. His restlessness and frequent shouts of pain were relieved by the intravenous administration of amytal solution. Examination at this time revealed a rectal temperature of 97.6° F., pulse 125, respirations 32, and blood pressure in mm. of mercury 130 systolic and 95 diastolic. The cutis marmorata was a deep purple and extended from the toes to the lower abdominal wall, the scrotum and the buttocks. The skin of both lower extremities was cool from the groin to the toes. No pulsations in the major vessels of either lower extremity could be felt.

The laboratory data were: hemoglobin 79 per cent, red blood cells 4.0 m., white blood cells 13,800, polymorphonuclear leukocytes 96 per cent, lymphocytes 2 per cent, monocytes 2 per cent. The urine had a specific gravity of 1.022 and contained a considerable amount of protein, sugar and acetone. The blood sugar was 211 mg. per cent, urea 25.8 mg. per cent and carbon dioxide combining power 53 volumes per cent. Oscillometric readings taken at various levels from the foot to the groin failed to show patency of the vessels of either lower extremity.

The clinical impression was that of occlusion of the abdominal aorta at its bifurcation. After 16 hours both femoral arteries were opened. The vessel walls were found to be thickened and sclerotic. Cork screw platinum probes were introduced into the lumina of the vessels for a distance of several inches and withdrawn, but no thrombus or part of the thrombus or blood followed the removal of the probe. The vessels were closed and the wounds were sutured.

The patient was returned to his room and 5000 units of liquaemin * in normal saline were administered intravenously. The pulse was rapid and feeble. Râles were audible throughout both lung fields. The patchy cyanosis of the extremities was replaced by a diffuse cyanosis. The temperature rose to 105.8° F. The blood pressure in mm. of mercury was 90 systolic and 70 diastolic. His condition grew rapidly worse and death occurred 33 hours following the onset of the acute vascular attack.

The anatomic diagnoses were: arteriosclerosis generalis; myomalacia cordis; mural thrombus in the left ventricle; dilatation of the heart; thrombus in the ab-

* The liquaemin was supplied by Roche-Organon, Inc., Nutley, New Jersey.

dominal aorta, external and internal iliac arteries with occlusion; thrombi in branches of the pulmonary artery; infarcts in the lungs; focal bilateral pneumonia; and infarct of the left kidney.

The pertinent findings at autopsy were as follows. The heart weighed 290 gm. The anterior wall of the left ventricle in the region of the apex appeared to be bulging, and the overlying epicardium was dull. The foramen ovale was patent. There was a sharply demarcated, slightly elevated, bizarre-shaped area in the myocardium of the septum and left ventricle at the apex which measured 4 by 1.5 cm. and was surrounded by a bright red border. There were numerous irregularly shaped friable blood clots on the endocardium overlying this area. Numerous smaller blood clots which were firmly adherent to the wall were present in between the rather widely separated trabeculae carneae. Many soft, irregularly shaped yellow deposits were present in the ascending part of the aorta and in the aortic leaflet of the mitral valve. The coronary arteries were tortuous. Their walls were markedly thickened and the lumina were narrowed by the deposition of firm calcified material. A lumen of the anterior descending branch of the left coronary artery could hardly be made out.

The abdominal aorta (figure 1) as well as both external and internal iliac arteries

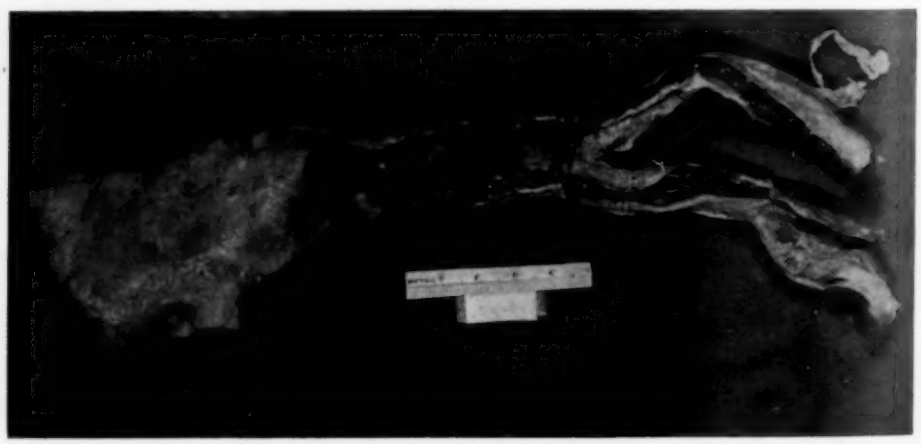

FIG. 1. The abdominal aorta (case 1) was occluded by the clot which extended into both iliac arteries.

were filled with a friable blood clot, which in places was attached firmly to the wall. It reached 9 cm. above the bifurcation to the level of the inferior mesenteric artery. The intima of the aorta contained numerous soft yellow plaques. The walls of the femoral arteries were markedly thickened. In a cross section of the abdominal aorta, the intima was thickened. The endothelial lining cells were missing in areas and these roughened surfaces were covered by irregular thrombotic masses. The adventitia was normal. In cross sections from the left iliac artery, the right iliac artery and right femoral artery, the microscopic picture was similar to that present in the aorta. Additional findings included infarction of the left kidney and the lungs.

Comment. Though the diagnosis of occlusion of the abdominal aorta was made, surgical intervention was not undertaken until 14 hours had elapsed. This time interval, as suggested by Fry[7] and emphasized by Ravdin and Wood,[8] proved to be too long. The history of the sequence of events preceding the onset of the catastrophic terminal illness was so atypical

as to be misleading. Therefore, the presence of myocardial infarction was not suspected. In the light of the postmortem findings, it was evident that the absorption of blood elements which followed the myocardial infarction was the explanation for the mild jaundice. In spite of the marked generalized arteriosclerosis, it was felt that an embolus rather than a thrombus occluded the lumen of the aorta. This was based upon the fact that the mural thrombus, which was found on the portion of the endocardium of the left ventricle whose blood supply came from the occluded anterior descending branch of the left coronary artery, had a rough, bright, friable surface over its lower portion. The 5,000 units of liquaemin employed were equivalent to 2.5 c.c. At the time of administration heparin was a comparatively new drug and dosage schedules were not well established. The amount used represented about 12.5 mg. of the sodium salt of heparin, whereas now in the average case a daily dose of 300 mg. or more is given. It is questionable, therefore, whether the amount of heparin used had any effect.

Case 2. A 78 year old white man with evidence of prostatism and a cough of long duration was seized with a sudden attack of pain in the right upper abdomen radiating to the angle of the right scapula. It was not associated with nausea or vomiting. Three days after the onset of this episode, a mass appeared in the right lumbar region. On aspiration, a purulent fluid which was sterile on culture was obtained.

The pertinent physical findings were: temperature 99.8° F., pulse 98, respirations 20, blood pressure in mm. of mercury 150 systolic and 100 diastolic. The patient was dehydrated and appeared chronically ill. The chest was emphysematous. The heart tones were distant and of poor muscular quality. Frequent extrasystoles were audible. The right flank was more prominent than the left.

Laboratory data: hemoglobin 62 per cent, red blood cells 2.89 m., white blood cells 2,900, polymorphonuclear leukocytes 37 per cent, band forms 15 per cent, lymphocytes 38 per cent, monocytes 2 per cent, and eosinophiles 5 per cent. The urine was normal. The blood sugar, urea and carbon dioxide combining power were normal. The erythrocyte sedimentation rate (Westergren method) was 63 mm. in 1 hour. An intravenous urogram revealed normal kidney function; a conventional teleroentgenogram revealed moderate cardiac enlargement. The electrocardiogram revealed left axis deviation and myocardial damage. The sternal marrow picture was not specific.

The patient developed ascites. The anemia and leukopenia became more pronounced. A paracentesis abdominalis yielded 5 liters of clear fluid in which no neoplastic cells were demonstrable. The course was steadily downward and death occurred 22 days after his admission to the hospital.

The anatomic diagnoses were miliary tuberculosis of the lymph nodes, the peritoneum, the spleen, the pleura, the lungs, and the liver; arteriosclerosis generalis; cardiac hypertrophy; myofibrosis cordis; thrombus in the aorta; abscess in the stomach; cholecystitis; and cholelithiasis.

The pertinent autopsy findings were as follows. The peritoneal cavity contained approximately 2000 c.c. of a clear greenish fluid. The omentum was thicker than usual. The peritoneal surfaces, including the omentum, visceral and parietal peritoneum, mesentery, serous coats of the bowel and peritoneal reflection of the diaphragm, were studded with discrete, gray-white firm plaques which measured up to 0.5 cm. in diameter, were slightly raised above the surface, and were difficult to cut. The right pleural cavity contained 450 c.c., and the left 250 c.c. of fluid similar to that found in the peritoneal cavity. The parietal pleura was studded with nodules similar to those described above but smaller in size.

The heart weighed 430 gm. The lower part of the lumen of the left ventricle was occupied by an irregular, firm, gray-white substance which was adherent to the posterior wall of the ventricle and the interventricular septum. When this substance was removed the underlying endocardium was gray-white in color and thinner than the remaining, unaffected wall. The coronary ostia were patent. The coronary vessels were markedly sclerotic and contained numerous atheromatous patches. The ascending and descending aorta were the seat of numerous, large, calcific, atheromatous plaques many of which were ulcerated. Five cm. distal to the orifices of the renal arteries there was a globular distention of the aorta (figure 2), the lumen of which was filled with a rubbery, gray-white mass which was adherent to the vessel wall.

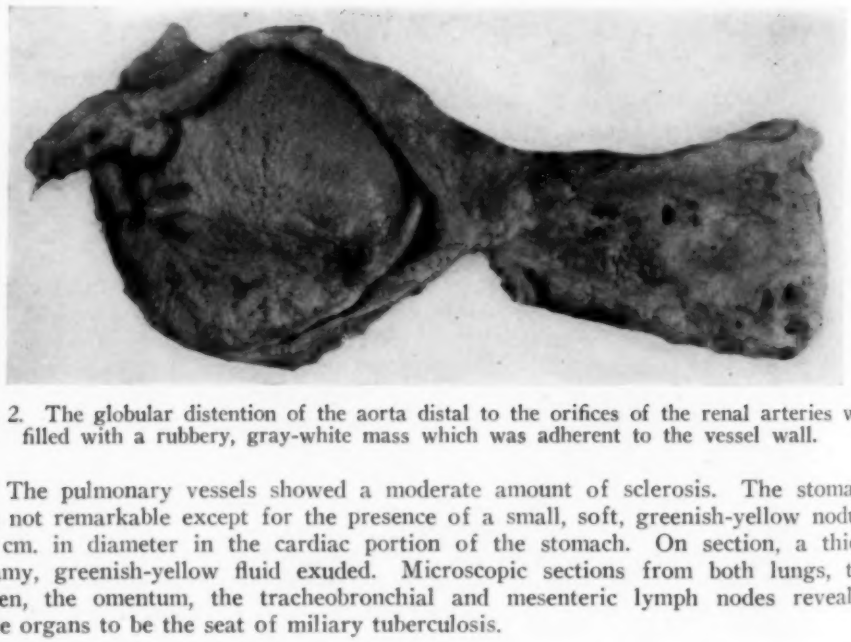

FIG. 2. The globular distention of the aorta distal to the orifices of the renal arteries was filled with a rubbery, gray-white mass which was adherent to the vessel wall.

The pulmonary vessels showed a moderate amount of sclerosis. The stomach was not remarkable except for the presence of a small, soft, greenish-yellow nodule 0.4 cm. in diameter in the cardiac portion of the stomach. On section, a thick, creamy, greenish-yellow fluid exuded. Microscopic sections from both lungs, the spleen, the omentum, the tracheobronchial and mesenteric lymph nodes revealed these organs to be the seat of miliary tuberculosis.

Comment. This patient had miliary tuberculosis involving the lymph nodes, peritoneum, pleura, lungs, liver and spleen. The thrombus which was found in an aneurysm of the abdominal aorta formed on an arteriosclerotic plaque in the lumen of the aorta and incompletely occluded the vessel. There were no symptoms during the life time of the patient which would have focused attention on the lesion in the aorta. There was a mural thrombus found in the left ventricle at the site of an old occluded coronary artery, which was in no way responsible for the thrombus which was present in the aortic aneurysm. A type III pneumococcus was grown in pure culture from the pus evacuated from the abscess which was found in the stomach wall.

Case 3. A 43 year old white man, with a history of a duodenal ulcer and syphilis which had been adequately treated, was admitted following the sudden onset of pain in the epigastrium and vomiting. The pertinent findings on physical examination

included: temperature 101.2° F., and blood pressure in mm. of mercury 198 systolic and 88 diastolic. The pupils reacted to light and accommodation. A soft low-pitched aortic diastolic murmur was audible at the right of the sternum. Abdominal rigidity which was most marked in the epigastrium was present.

Laboratory data: hemoglobin 107 per cent, red blood cells 5.1 m., white blood cells 17,500, polymorphonuclear leukocytes 90 per cent, band forms 22 per cent, lymphocytes 6 per cent, monocytes 4 per cent. The urine contained albumin, sugar, and acetone, and occasional white blood cells. The blood Wassermann and Kline tests were negative. The erythrocyte sedimentation rate and blood chemistry were normal. A flat plate of the abdomen revealed distention and fluid levels in the loops of the small intestine. There was no free gas under the diaphragm. The barium enema was normal. The barium meal showed an irregularity in the caliber of the small intestine. The conventional teleroentgenogram was normal.

Fecal vomiting was present on the second day. The hospital course was progressively downward. Universal abdominal rigidity developed. The temperature continued to rise and the terminal picture was that of peritonitis. Death occurred 14 days after his admission to the hospital.

The anatomic diagnoses were: volvulus of the small intestine with gangrene, peritonitis, bronchitis, pneumonia, arteriosclerosis generalis, aneurysm of the abdominal aorta with mural thrombus, thrombus in the aorta and common iliac arteries, hypertrophy and dilatation of the heart.

The pertinent autopsy findings were as follows. On opening the peritoneal cavity, air escaped. The peritoneal surface was covered by a plastic, gray-green exudate. There were many fibrous and fibrinous adhesions between the loops of intestine. The omentum was in its normal position. There were more than 1,000 c.c. of thick, creamy, gray-green pus in the peritoneal cavity. A collection of thick, gray-green exudate which bathed 40 cm. of completely necrotic and unattached small intestine was found behind the terminal portion of the ileum. The proximal and distal portions of this loop of ileum opened into the peritoneal cavity. The remainder of the intestinal tract showed nothing of note.

The heart weighed 430 gm. The walls of the coronary arteries were thickened; the intima of the thoracic aorta contained many soft and firm yellow plaques. Immediately above the origin of the renal vessels, the wall of the aorta bulged out. Attached to the intima in this pocket was a firm thrombus which extended downward beyond the bifurcation of the aorta into the iliac arteries. The microscopic picture of a section taken from the aorta was that of a syphilitic aortitis.

Comment. The volvulus of the small intestine which went on to gangrene formation with a fulminating peritonitis completely clouded the picture found in the aorta at necropsy. In spite of the negative serologic reactions, the microscopic appearance of the section taken from the aorta revealed that vessel to be the seat of a syphilitic aortitis. The thrombus formed in the aneurysm and extended beyond the bifurcation of the aorta into the iliac arteries. There were no localizing signs during the stormy terminal illness which would have suggested the diagnosis of occlusion of the aorta.

Case 4. A 67 year old white man who had a peptic ulcer noted increased difficulty in starting the urinary stream, voided small amounts of urine frequently, and complained of dysuria. Acute urinary retention developed and hospitalization was advised.

The pertinent physical findings were: temperature 99.2° F., pulse 108, respirations 22, and blood pressure in mm. of mercury 136 systolic and 88 diastolic. The thorax was deformed as a result of a marked scoliosis. The lungs presented evidence of

early congestive heart failure. The heart was normal in size. A soft systolic murmur was audible at the apex. There were bilateral inguinal herniae. On rectal examination the prostate gland was enlarged.

Laboratory data: hemoglobin 67 per cent, red blood cells 4 m., white blood cells 13,200, polymorphonuclear leukocytes 70 per cent, lymphocytes 25 per cent, band forms 12 per cent, monocytes 2 per cent, eosinophiles 1 per cent. The urine and blood chemistry were normal. The erythrocyte sedimentation rate (Westergren method) was 30 mm. The Wassermann reaction was negative.

On the tenth day, the patient had a chill with an elevation of temperature to 102° F. The urine contained a trace of protein and many clumps of pus cells. Two days later, his blood pressure dropped to 76 mm. Hg systolic and 60 mm. diastolic, and the patient was drowsy. Showers of fine râles with impaired resonance were present at the base of the left lung. There was a leukocytosis of 30,000 with 90 per cent polymorphonuclear leukocytes. Roentgenographic examination confirmed the presence of bronchopneumonia. The electrocardiogram showed right axis deviation. Four days later a left facial palsy and weakness of the left hand were noted. The blood urea nitrogen was 53.5 mg. per cent. He became markedly dyspneic and cyanotic. The heart rate was extremely rapid. Generalized muscular twitchings developed, and the patient died on the twenty-first day after his admission to the hospital.

The anatomic diagnoses were: arteriosclerosis generalis; mural thrombus in the aorta, infarction of the kidneys; cardiac dilatation, atelectasis of the lung, stomach ulcer and argentaffin cell tumor of the jejunum.

The pertinent autopsy findings were as follows. The heart weighed 280 gm. The coronary arteries were opaque, firm, gray and tortuous. The aorta was the seat of marked sclerotic changes. The intima contained numerous raised, firm, yellow and gray sclerotic plaques. The elasticity was markedly impaired. A firm, brown blood clot was found adherent to and embedded in a slight outpouching (figure 3) of the

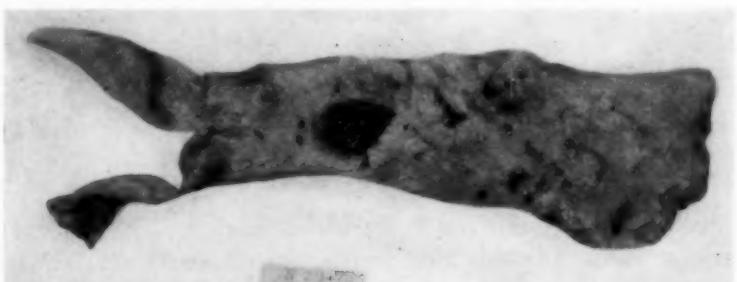

FIG. 3. Photograph of the fixed specimen of the abdominal aorta in case 4 showing the contracted clot which was embedded in the outpouching of the aorta.

aorta 3 cm. above the bifurcation. The free surface of the thrombus completely occluded the lumen of the aorta. There were many nonperforating ulcers along the lesser curvature of the stomach near the pylorus. The bladder was the seat of an acute cystitis. The prostate gland was enlarged.

Comment. The mural thrombus which was found in the aorta had formed on a sclerotic plaque in the vessel wall. The presenting symptoms were those of urinary sepsis with renal failure. There was nothing in the history to suggest impaired circulation below the point of obstruction.

Case 5. A 41 year old white woman, with a history of intolerance to greasy and fried foods, had a recurrent attack of nausea, vomiting and belching. During this attack, which lasted three days, jaundice, constipation, and loss of appetite were noted.

The pertinent findings on physical examination were: temperature 101.9° F., pulse 110, respirations 22, blood pressure in mm. of mercury 150 systolic and 90 diastolic. The sclerae and skin were icteric. There were signs of congestion at the bases of both lungs. The liver was palpable four fingers' breadth below the costal edge.

Laboratory data: hemoglobin 67 per cent, red blood cells 3.89 m., white blood cells 18,600, polymorphonuclear leukocytes 78 per cent, lymphocytes 9 per cent, band cells 9 per cent, monocytes 4 per cent. The urine, aside from containing bile pigments, was normal. The erythrocyte sedimentation rate (Westergren method) was 35 mm. in 1 hr. The blood sugar and urea were normal. The total cholesterol was 218 mg. per cent; the free cholesterol was 127 mg. per cent; the cholesterol esters 58 mg. per cent; the phosphorus 2.2 mg. per cent; phosphatase 7.5 Bodansky units; the direct van den Bergh was positive and the indirect was 24.8 units. The stool contained bile.

Her course was progressively downward. The jaundice increased. The patient became confused mentally, developed signs of bronchopneumonia, and died after going into circulatory collapse on the seventh day after her admission to the hospital.

The anatomic diagnoses were yellow atrophy of the liver, cholemic nephrosis, dilatation of the heart and thrombosis of the aorta.

The pertinent autopsy findings were: the skin and sclerae were yellow. The heart weighed 245 gm. The coronary ostia and coronary arteries were patent. The elasticity of the aorta was not impaired. A thrombus which completely occluded the aorta was found adherent to the intima at the bifurcation. It extended into the common iliac arteries for a distance of 5 cm. The liver and spleen were both enlarged. The kidneys showed evidence of a cholemic nephrosis.

Comment. The thrombus found in the aorta was adherent to an area in the intima which was the seat of a calcified plaque. The terminal picture which was typical of an acute yellow atrophy of the liver completely obscured the presence of a thrombus in the aorta.

Discussion

Thrombosis and embolism of the abdominal aorta are relatively infrequent catastrophies which occur in individuals with chronic vascular and chronic valvular disease. The rôle of the chemical, colloidal, and physical changes which take place in the blood, together with the rôle of injury to the endothelial cells of the intima and the rôle which stasis plays in the formation of thrombi, have been a matter for much speculation, a discussion of which is beyond the scope of this presentation. Though adequate studies of the factors which may increase the coagulability of the blood during the course of infectious diseases have not been made, Hunter [9] believed that occasionally thrombi resulted from the action of bacterial toxins on the endothelial cells of the intima. Manasci,[10] Bodeff,[11] Moschcowitz,[12] Wheeler,[13] and Rothstein [6] cited instances in which sudden occlusion of the abdominal aorta occurred during the course of infectious diseases. Retrograde thrombosis may occur and may extend upward to involve the aorta from a distant traumatized

vessel. Thrombosis may also occur in arteriosclerotic vessels (cases 2 and 4) or in an aorta which is the seat of chronic vascular disease such as thromboangiitis obliterans or syphilis (case 3). In the former, the thrombus may form on an atheromatous plaque or at the site of a roughened intima, whereas in the latter the occlusion is usually at the site of a chronic inflammatory process.

There are many sources from which emboli which occlude the abdominal aorta may take their origin. When disease of the heart is present, and particularly if such disease is associated with disturbances in rhythm, sudden occlusion of the aorta can usually be attributed to an embolus of central origin. In the presence of a patent foramen ovale, an embolus to the aorta may take its origin in either the right side of the heart or from the site of a thrombophlebitis. Rheumatic heart disease, chronic congestive failure, auricular fibrillation, myocardial infarction and coronary artery thrombosis are associated with a high incidence of mural thrombi. These thrombi, which may be flat or polypoid, are usually found in the recesses of the heart where the circulation is slowest. A portion of such a mural thrombus may become detached from its base and pass with the general blood stream to the point of arrest. Thrombi in the walls of the aorta may be responsible for emboli to some distant point. The ball valve thrombus of the auricle, which according to Garvin [14] is extremely rare, may also be the starting point for an embolus to the aorta.

Incidence. The relative infrequency with which the abnormality under discussion occurs may be judged by reviewing its incidence as reported from several hospitals. Thrombosis and embolism of the abdominal aorta were found but once in 1047 consecutive postmortem examinations made at the Research and Educational Hospitals of the University of Illinois.[15] Siegal and Garvin [16] found 11 cases of abdominal aorta thrombosis in their review of 6547 autopsies performed at the Cleveland City Hospital. Seven cases were found in a study of 5350 necropsies reviewed by Philips and Gross [17] at the Montefiore Hospital in New York City. The five cases reported in this communication represent the number found in 3991 consecutive autopsies performed at the Jewish Hospital of Brooklyn.

Distribution. Embolism of the abdominal aorta appears to occur with equal frequency among men and women, but the ratio of males to females who have thrombosis of the aorta is about 2 : 1. Thrombosis and embolism of the abdominal aorta occur at all ages. The earliest recorded case of thrombosis of the abdominal aorta was that of the 10 day old infant with an umbilical cord infection reported by Moschcowitz.[12] The majority of cases, however, have occurred in individuals in the fourth and fifth decades of life.

Symptoms. The most alarming aspect of the symptomatology of thrombosis and embolism of the abdominal aorta has been emphasized in dramatic language. In spite of the fact that the usual clinical picture is ushered in with symptoms which are sudden in their onset, the acute episode

has occasionally been overlooked because the characteristic pain as a major symptom has been absent.[18]

On the basis of the symptomatology, cases of abdominal aorta obstruction may be classified into two general groups, i.e., those in which the symptoms are slow in their onset and those in which the onset is sudden. The gradual onset of pain speaks in favor of a gradually narrowing process. In this group of patients a careful history may elicit evidence of intermittent claudication which is most often situated in the arch of the feet or in the calf muscles of the legs. If the occlusive arterial disease extends up as far as the femoral arteries, these symptoms may even be referred to the thighs or the hips. Color changes, disturbances of sensation and a gradually increasing coldness of the extremities may be present. A sudden change in this picture means the completion of the occlusion. In a thin individual, direct palpation may reveal absent pulsations of the abdominal aorta below the point of occlusion and occasionally dilatation of the aorta above the upper limit of the thrombus. With the onset of gangrene, the pain becomes constant and is severe. The extent of the gangrene will depend upon the completeness of the occlusion and the status of the collateral circulation.

In sharp contrast to the gradual progression of symptoms which perhaps occur more frequently with thrombosis is the sudden onset of agonizing pain usually referred to both lower extremities when the lesion is embolic. Occasionally the pain may be referred to the abdomen, the inner aspects of the thighs, the scrotum, the sacrum, the small of the back, the loin or the perineum. Sudden collapse accompanied by a cold and clammy perspiration may be followed by evidence of interference with the circulation of both lower extremities. The pain may be constant or paroxysmal. Coldness, numbness, pallor, and complete loss of sensation develop rapidly. Partial or complete paraplegia may be present. Cyanosis accompanied by mottling of the skin is often followed by gangrene. Pulsations of the major vessels of the lower extremities are altered and, depending upon the completeness of the occlusion, these pulsations may disappear promptly in both lower extremities or first in one extremity and then in the other. Urgency and frequency, vesical and rectal tenesmus, vomiting and diarrhea have been noted. Oscillometric readings from the dorsalis pedis artery to the femoral artery are either absent or are greatly diminished depending upon the completeness of the blockage. The skin surface temperature is definitely reduced. After a short interval gangrene develops, varying with the extent of the blockage and the state of the collateral circulation.

Differential Diagnosis. Though the classical syndrome may include the sudden onset of severe pain, loss of sensation in both lower extremities, absence of pulsations extending all the way up to include the femoral arteries, and a rapidly developing ascending gangrene with an ultimately fatal outcome, Philips and Gross [17] have reëmphasized the fact that this sequence of events is often not present. Widespread venous thrombosis of both lower

extremities has been mistaken for thrombosis of the abdominal aorta. In contradistinction to the coldness, pallor, loss of sensation and of arterial pulsations, absence of edema and the development of a dry gangrene in occlusion of the abdominal aorta, cases of venous thrombosis have warm, cyanotic, edematous extremities in which arterial pulsations may be identified depending upon the extent of the edema. Sensations are often unchanged and tender veins are usually present. If facilities are available, the intravenous use of a contrast substance for visualization of the vascular tree may be of differential diagnostic value.[2, 19]

Ischemic necrosis, occasionally seen in patients with advanced arteriosclerosis of the vessels of the lower extremities, should not be confused with the gangrene which develops following the dramatic onset of the vascular catastrophe under discussion. Simultaneous complete occlusion of both common iliac arteries may present a perplexing differential problem. Absent pulsations of the vessels of the lower extremities may occur in the presence of severe anemias, thromboarteriosclerotic disease of the vessels of the lower extremities, thromboangiitis obliterans, coarctation of the aorta, and extensive thrombophlebitis with reflex vascular spasm. Thickness of the skin in diseases such as scleroderma may interfere with the identification of main stem arterial pulsations of the vessels of the lower extremities. However, the patchy distribution of the skin lesions and the other stigmata of scleroderma should be of value. Functional circulatory disturbances are not likely to be confused with embolism.

Prognosis. The prognosis is always grave. Hess [20] showed that 95 per cent of the 73 cases which he collected died under conservative therapy. Rothstein [6] found that 112 patients or 91 per cent of the 123 reported up to 1935 proved fatal. Since then, 33 additional case reports have been added to the steadily growing literature. Of these, three patients were operated upon successfully and survived from six months to beyond three years. The total number of cases including those contained in this communication is now 161. Of these 147 or 91.3 per cent were fatal. Death occurred anywhere from within several hours to six months after the onset of symptoms. Those who live either develop an adequate collateral circulation without operative intervention or dislodge the embolus from the bifurcation of the aorta into one of the iliac arteries with resulting amputation of part of the extremity. A small number of patients recover following embolectomy with gangrene and partial amputation or following embolectomy without gangrene. Kerr's [21] patient survived embolectomy on two separate occasions and finally succumbed following an acute coronary artery occlusion.

Treatment. The diagnosis of occlusion of the aorta is not difficult when gangrene is obvious but treatment at that stage is futile. The diagnosis must be made early if treatment is to be of value. In the great majority of cases, occlusion of the abdominal aorta occurs in individuals with preëxisting cardiac disease. The treatment, therefore, is sharply divided into two parts. The first is the treatment of the cardiac disease and the second is the treat-

ment of the aortic obstruction. Although the former is beyond the scope of this presentation, the latter may be either conservative or radical. The success of conservative therapy depends upon evidence of a progressively improving circulation. The decision as to whether to persist with conservative therapy depends upon evidence of a progressively improving circulation. Watchful waiting may offer as a reward the development of a sharply demarcated gangrenous area which may subsequently be treated surgically. Tingling of the toes after the appearance of numbness usually signifies returning blood supply and warrants the continuation of expectant treatment. Partially occlusive bandages, Buerger's exercises, the oscillating bed, tissue extracts, alcohol and papaverine may occasionally be used to advantage to promote the establishment of collateral circulation. Heparin has been used successfully by Ravdin and Wood [8] to prevent recurrence and distal propagation of the thrombus. If heparin is used, it is important to remember that the addition of minimal amounts of protamine will inactivate the heparin when one wishes to bring the coagulation time back to normal. Surgery should be employed early because changes in the intima at the site of the occlusion may form the starting point for additional thrombi despite the postoperative use of heparin. Delay in surgical intervention due to incorrect or hesitant diagnosis may necessitate partial amputation or may be responsible for a fatal termination. The surgical procedures employed include aortotomy and iliac or femoral arteriotomy with extraction of the clot. Resection of the occluded portion of the aorta together with lumbar sympathectomy have been performed. Paravertebral sympathetic block may be of value in relieving vascular spasm distal to the arterial obstruction.

Summary

The classical syndrome of obstruction of the abdominal aorta is one which is sudden in its onset and has been associated with a well delineated group of symptoms including severe pain and loss of sensation in the lower extremities, absence of arterial pulsations, progressive ascending gangrene, and finally death. Five proved cases of occlusion of the aorta were studied. Four of the aortas were occluded as a result of a thrombus. In one case an embolus which had its origin in a mural thrombus was deposited at the bifurcation of the aorta and occluded it. All of the patients had evidence of generalized arteriosclerosis. In the case of the embolus, the mural thrombus formed on the wall of the ventricle in the portion of the muscle supplied by the occluded anterior descending branch of the left coronary artery. Three of the cases of thrombosis of the aorta occurred in men and one in a woman. The men were in a much higher age group, though all four cases occurred in individuals beyond the fourth decade of life. The classical uncomplicated clinical picture usually associated with complete occlusion of the abdominal aorta at its bifurcation was present only in the first case. Though thrombi which occluded the aorta were found at postmortem examination

in the remaining four cases, there was nothing in the clinical course to suggest involvement of the aorta.

Conclusion

1. A case of embolism of the abdominal aorta is reported.
2. The association of miliary tuberculosis, peritonitis, urinary sepsis and yellow atrophy of the liver with thrombosis of the abdominal aorta was noted.
3. Variations from the classical clinical syndrome of occlusion of the abdominal aorta were cited.
4. Five additional cases of occlusion of the abdominal aorta were added, making the total number of cases now on record 161.

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CASE REPORTS

CARCINOMA OF THE ISLANDS OF LANGERHANS WITH LIVER METASTASIS PRODUCING HYPERINSULINISM *

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This case is being reported because of the apparent rarity of the condition and the fairly typical clinical course exhibited. A review of the literature up to the time this paper was written revealed only 13 [1] similar cases reported in man, seven of which had either lymph node or liver metastasis or both. This patient presented the usual clinical picture associated with hyperinsulinism.[2] It is to be regretted that a biological assay for insulin was not made of the metastatic nodules in the liver, as has been shown by Powers and Wilder to be conclusive proof of the origin of these tumors. However, the pathological lesions and clinical symptoms in this patient were so typical that it is felt the diagnosis was evident.

Case Report

Clinical History. K. R., a white male, aged 36 years, a painter and decorator, was first seen January 20, 1937, because of frequent attacks of unconsciousness. The onset of his illness dated from August 15, 1936, following an alcoholic debauch on a hunting trip, during which he drank one to two pints of whiskey. On returning to his car, he lay down on the front seat where he lost consciousness for about two hours. Recovering spontaneously from this, he felt very weak and dizzy, but after eating, he felt normal. Two weeks later, after feeling perfectly well during the interim, he had another attack of unconsciousness without the antecedent alcoholic debauch. Subsequent attacks occurred every week or more. He could tell when these were coming on by a fluttering sensation in the abdomen. This sign, however, finally disappeared. Attacks usually occurred about 11:00 a.m. He never lost control of his sphincters. The attacks occurred more commonly after a period of physical effort but never after a period of rest. Usually he was able to walk to the house or car with a little help after the attack started and even then was able to swallow satisfactorily. This was usually followed by profuse diaphoresis. The only significant features of his past history were: an attack of polyarthritis at the age of eight, which kept him in bed for eight weeks; an accident at the age of 21 when he fell from the fourth floor of a building without losing consciousness; and another accident at the age of 35, when he fell off a porch onto his head, losing consciousness for only a few minutes. He had always been a somewhat heavy drinker.

Physical Examination. Temperature was 98.4° F., pulse 60–64, respirations 36, and blood pressure 110 mm. Hg systolic and 64 mm. diastolic. Otherwise routine physical examination and complete neurological examination were entirely normal.

Laboratory Findings. Urine was negative. Erythrocyte count was 4,700,000 with 14 grams hemoglobin (Newcomer); leukocyte count 9,050 with 74 per cent polymorphonuclears, 22 per cent small lymphocytes, 1 per cent monocytes, 2 per cent metamyelocytes and 1 per cent nonsegmented neutrophiles. The Kline and Kahn

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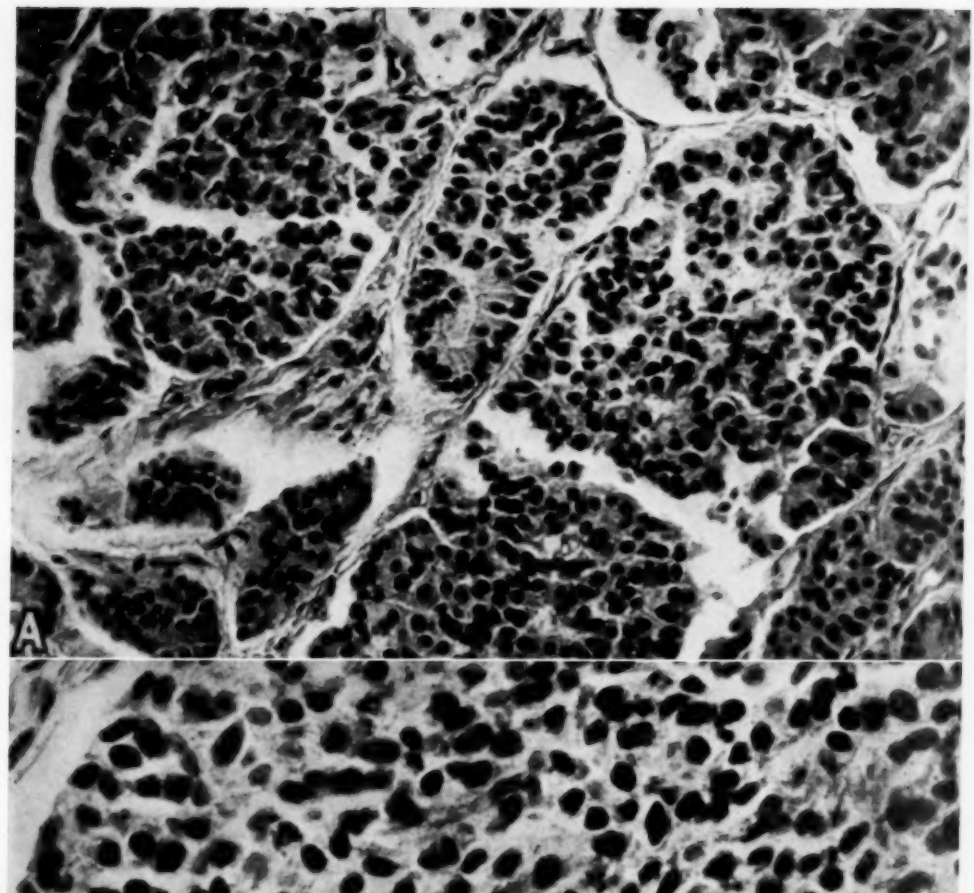

FIG. 1. (*A*) Section of tumor of pancreas.
(*B*) Section of lymph node adjacent to pancreas, showing metastasis.

tests were negative. Blood sugar on admission was 52 mg. per cent. Glucose tolerance test (100 grams of glucose by mouth) showed: fasting, 35 mg. per cent; one half hour, 104 mg. per cent; one hour, 121 mg. per cent; two hours, 106 mg. per cent; and three hours, 90 mg. per cent. Blood calcium was 10.4 mg. per cent. Spinal fluid examination on admission showed no cells, no globulin, and sugar 25 mg. per cent. Roentgenologic examination of chest and skull, and encephalogram were normal.

Clinical Course. The glucose tolerance test and the general characteristics of the attacks suggested the possibility of paroxysmal hypoglycemic reactions due to hyperinsulinism. He was requested to fast for a period of 24 hours. Within about 12 hours, however, he became unconscious, with generalized tonic and clonic convulsions and rather profuse diaphoresis. The blood sugar at this time was 18 mg. per cent. After 50 grams of glucose were administered intravenously, the patient rapidly regained consciousness and asked, "What happened?" This procedure was repeated with similar results. Repeated fasting blood sugar determinations were as follows: 35 mg. per cent, 48 mg. per cent, and 40 mg. per cent. He was maintained on a diet high in carbohydrate and protein, containing approximately 3,000 calories daily.

Exploration of the pancreatic tissue was deemed advisable in view of the following: (a) absence of any extrapancreatic causes of hypoglycemia, (b) repeated fasting blood sugars below 50 mg. per cent on an adequate diet, (c) several blood sugars below 40 mg. per cent which in some instances were associated with convulsive seizures that responded to the administration of glucose intravenously. On February 12, 1937, surgical exploration of the abdomen was performed revealing multiple small hard nodules in the pancreas which were interpreted by the surgeon to be due to inoperable carcinoma. There was one small metastatic nodule observed in the liver which was removed for biopsy (Section C). His operative convalescence was uneventful, his hypoglycemic reactions being fairly well controlled by diet and intravenous glucose. His course during the next year was rather stormy, requiring at least three admissions to the hospital for control of hypoglycemic reactions, in spite of attempted control at home with special diet and frequent feedings of sweetened orange juice when attacks occurred.

His last hospital admission was on April 8, 1938, because of a hypoglycemic reaction, in which the blood sugar was 12 mg. per cent. He responded to intravenous glucose satisfactorily but while in the hospital developed scarlet fever and, in spite of intravenous scarlet fever antitoxin and other supportive therapy, died three days after the onset of scarlet fever with apparent circulatory failure and terminal pulmonary edema.

Necropsy. The chief findings at the postmortem examination were in the liver and pancreas. The pancreas weighed 174 grams. There was a nodular tumor mass, measuring 9 cm. in diameter, occupying the body of the pancreas and displacing the tissue in the proximal portion. The tail of the pancreas was diffusely infiltrated with tumor tissue and no recognizable normal pancreatic tissue remained. The proximal portion of the head of the pancreas appeared normal. The distal portion of the head was infiltrated by tumor tissue. In all a nodule of pancreatic tissue measuring about 4 cm. in diameter had a relatively normal appearance. Some of the adjacent nodes were greatly enlarged. The tumor tissue was of a firm consistency with a whitish homogeneous appearance.

The liver weighed 3,235 grams. The surface was smooth, but just beneath the surface were many irregular yellowish tumor nodules, measuring up to 4.5 cm. in diameter. On the cut surface the tumor nodules were found to be firm, with a faintly lobulated appearance. On section the largest nodule of the tumor tissue measured 8 cm. in diameter. Approximately two-thirds of the liver parenchyma was displaced by tumor tissue. The tumor nodules had a spherical contour with pinkish color. Some of the nodules showed scattered hemorrhagic areas.

The microscopic study of the tumor tissue of the pancreas (Section A) showed an atypical pattern with but few features of the normal gland. The tumor cells occurred in more or less compact masses varying greatly in size. The coarser masses were more numerous. Narrow, loosely organized connective tissue trabeculae separated the masses of tumor tissue. In none of these areas of tumor cells was there a definite acinar pattern. The cells were irregular in size and shape, and numerous atypical mitotic figures were found. Most of the nuclei were pyknotic and deep staining. The morphology of these cells and masses of tissue had all the characteristics of cells described in previous reports,[1] said to have had their origin from islet cells and shown by biologic assay to contain insulin. The cells in the lymph node adjacent to the pancreas (Section B) presented the same histological features. The enlarged photomicrograph (Section B) clearly demonstrates the cytology of

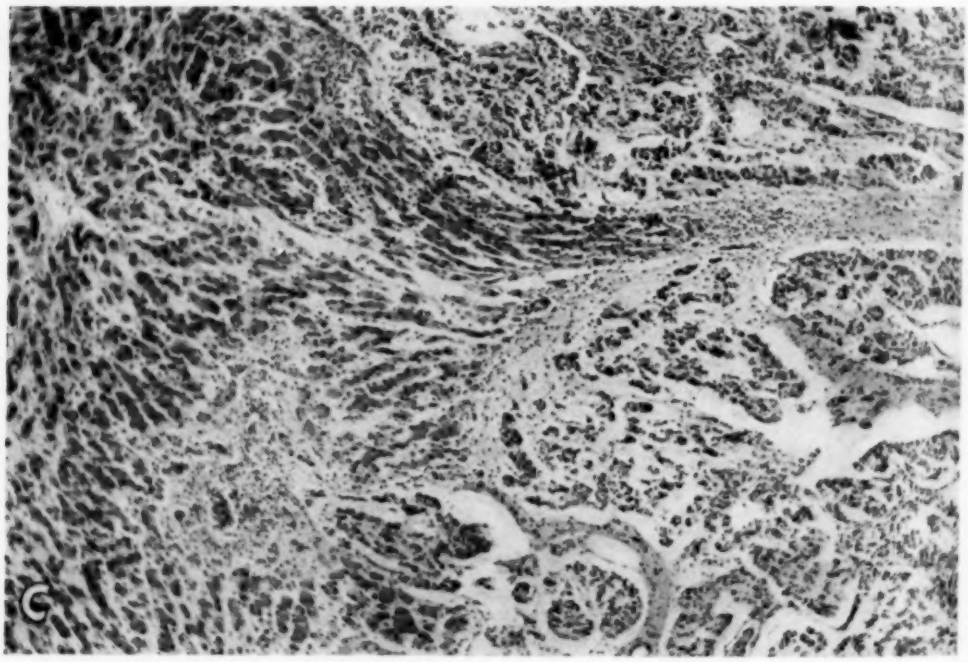

FIG. 1. (*C*) Section of metastatic nodule in liver removed at operation.

the tumor tissue. The metastatic nodules in the liver (Section C) had the same histologic structure as those in the pancreas and lymph node. Along the margins of the masses of tumor cells cord-like strands extended into the liver parenchyma. The cytoplasm of the tumor cells in both the pancreas and liver was very acidophilic. In no area were there any cell arrangements resembling acini or glandular structures, but rather they occurred in masses as described in the pancreas.

COMMENT

It is interesting that this patient could survive approximately 14 months after a positive diagnosis of inoperable metastatic islet cell carcinoma had been made. His hypoglycemic reactions were severe but were responsive to early treatment with glucose intravenously or sugar by mouth. One wonders whether an oper-

able tumor might have been found, as in a few previously reported cases, if this patient had presented himself when his symptoms first appeared.

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CHRONIC HEMOLYTIC ANEMIA WITH AUTOAGGLUTINATION AND HYPERGLOBULINEMIA; REPORT OF A FATAL CASE*

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The presence of any intravascular mechanism that destroys red cells in excess of bone marrow compensation results in an anemia of the hemolytic type.

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Any classification of the hemolytic anemias is difficult because of the large number and wide variety of agents that can destroy red cells. Among such agents are bacterial and parasitic infections, drugs, chemicals, animal poisons, and occasionally red cell destruction occurs as an allergic phenomenon as observed in sensitivity to the bean *Vicia fava* or the pollen of its flower. Chronic familial hemolytic icterus with spherocytosis, increased fragility of the red cells to hypotonic saline solutions and subsequent clinical cure by splenectomy is one of the more common types of hemolytic anemia in which the mechanism of hemolysis remains unknown.

The case reported in this paper is one of long standing, severe intravascular red cell destruction accompanied by reticulocytosis, numerous erythroblastic crises, splenomegaly, auto-agglutination and hyperglobulinemia. The cardinal features in this patient included a high amount of globulin in the blood from an unknown cause, accompanied by strong agglutination of her own cells as well as the cells of members of all blood groups. After many years of marked compensatory erythropoietic activity as indicated by reticulocytosis, her bone marrow became unable to compensate, and finally death occurred. We are unable to find an instance in the medical literature presenting the same features as seen in this patient.

The terms encountered in the medical literature denoting auto-agglutination are numerous and somewhat contradictory. Landsteiner was the first to distinguish clearly between *pseudo-agglutination* and *auto-agglutination*. His classification differentiates these conditions accurately and he distinguishes carefully between *pseudo-agglutination, cold* (*auto*) *agglutination,* and *iso-agglutination.*

Pseudo-agglutination may be designated as that condition in which there are varying degrees of rouleaux formation without subsequent hemolysis, which can be dispersed by agitation of the cell mixture. Errors in the determination of blood groups occasionally occur because of excessive rouleaux formation, and if this is marked it may simulate a true agglutination. It is most often seen in acute infections and is thought by some workers to be caused by increased viscosity of the blood serum.[3, 5, 6, 7] Slight dilution, as little as 1 : 3, dissipates this pseudo-agglutination. True iso-agglutination is not affected by agitation. The active principle in rouleaux is not absorbable, operates much more strongly at body temperature, is inactivated by dilution, and is non-specific. Cold agglutinins, on the other hand, become active at lowered temperatures and agglutinate the red cells of the same type and the same individual. For this reason these agglutinins have also been called auto-agglutinins. They are absorbable, withstand considerable dilution, and are non-specific.

Iso-agglutinins of human sera form the basis of determining the individual blood groups. When these agglutinins are mixed with cells containing the same agglutinogen, marked agglutination follows. They are called iso-agglutinins because of their specific action on blood cells of a subject of the same species. These iso-agglutinins are absorbable, are little affected by temperature change, withstand considerable dilution without becoming inactive, and indicate a specific blood group.

Reimann [3] first called attention to the "auto-hemagglutination" present in the blood of a patient being treated for arthritis. He observed that the red cells

of this patient underwent marked rouleaux formation on ordinary smears, in the red cell pipette and in the counting chamber when Hayem's solution was used as a diluent. This rouleaux formation led him to question the diagnosis of arthritis, and suspect hyperproteinemia secondary to multiple myeloma which was subsequently proved to be correct at necropsy. This rouleaux formation in his case was pseudo-agglutination instead of true auto-agglutination in the light of Landsteiner's classification. Jacobson [4] observed similar difficulties using Hayem's solution and determined that the precipitated substance belonged to the euglobulin portion of the blood protein and that euglobulin was precipitated by the bichloride of mercury which is one of the ingredients of Hayem's solution. Bonniger [5] reported similar observations but found no clumping of cells when salt solution was used as a cell diluent. Reimann,[3] Bonniger,[5] and Magnus-Levy [7] attribute the marked rouleaux formation to increased blood globulin and fibrinogen in their cases of multiple myeloma.

Antopol [8] and associates reported two cases of acute hemolytic anemia following neoprontosil therapy. Both of these patients were found to have blood of type O prior to the administration of the drug. After administration of the drug the first patient developed anemia, jaundice, and hematuria. The unwashed red cells were agglutinated by the patient's own serum and also the serum of groups A, B and O. This agglutination disappeared, however, when the preparation was heated to 37° C. The second patient also developed anemia and jaundice, and the serum agglutinated the patient's cells and other type O cells at room temperature, but the agglutination disappeared after incubation at 37° C. This appears to be an instance of cold agglutinins with corresponding hemolysins which became active after sulfanilamide therapy.

Hyperproteinemia has been observed in many chronic infections such as syphilis,[9] tuberculosis,[10] trypanosomiasis,[11] filariasis,[12] schistosomiasis,[13] sarcoid of Boeck,[14] lymphogranuloma,[15] kala-azar,[16] and multiple myelomatosis,[6] malignant tumors of the kidney,[17] and in lymphosarcoma.[18] In only one instance has it been reported in hemolytic jaundice,[19] and this was an "unexplained case" reported by Jeghers and Selesnick in which the total protein was 8.6 grams per 100 c.c. of blood with a globulin value of 4.5 grams and albumin of 4.1 grams.

Case Report

The patient was a white female, married, aged 32. She was admitted to the Emory University Hospital on January 16, 1940 with a chief complaint of weakness, and a prolonged history of a "peculiar" anemia that had been studied in many clinics with a variety of diagnoses.

Past History and Present Illness. Her childhood diseases included measles, mumps, chicken pox, and whooping cough without complications. The patient had always been well and had led a normal active life until the autumn of 1934. At that time she developed a mild fleeting arthritis involving the elbow, wrist, ankle, and finger joints, which never remained over 24 hours at one time. The involved joint would be painful on motion, slightly swollen, but never hot to palpation. She had had frequent upper respiratory infections during the winter, and had pneumonia during February of 1935 with a weight loss of five pounds. There were no further difficulties until August 1935, at which time weakness and fatigue on walking slowly developed and became progressively severe. She went to a sanatorium in England in September 1935 to gain strength, received symptomatic treatment, and was dismissed in November

as improved. Again in December 1935 there was an exacerbation of weakness and dyspnea on exertion. Constant bed rest was necessary because of weakness. She gradually improved, had an uneventful winter, developed pneumonia again in June 1936 and was brought to a New Haven, Connecticut, hospital. Here she was found to have a severe anemia accompanied by hepatomegaly and splenomegaly but no definite diagnosis was made. Gastric analysis at that time revealed free HCl. She improved after several weeks' rest, but had another relapse of weakness at which time a diagnosis of acute hemolytic anemia of Lederer was made. A transfusion was given but this was followed by chills, fever, and very dark urine. Radiation of the spleen was begun but discontinued because of a severe reaction. At this time a mild icterus was noted for the first time. A remission occurred after several weeks. She was dismissed from the hospital in March 1937, but continued to have weakness and symptoms referable to anemia along with a mild fleeting arthritis. At this time she had returned to England where transfusions were given on repeated occasions without improvement in the state of anemia. Absolute bed rest for a period of several weeks seemed the most effective way to bring about improvement. Another severe relapse occurred in May 1939 and a mild icterus was noted. She was then transfused four times with severe reactions following the last two. She gradually improved after a few weeks and had several months of good health. She then came to Miami, Florida, for the winter and had another relapse in November. A transfusion given there because of the severe anemia was followed by a severe reaction accompanied by oliguria, coma, and an elevation of the non-protein nitrogen of the blood to 150 mg. per cent. After several weeks she slowly improved and was brought to the Emory University Hospital in January 1940. She and her husband stated that each relapse was usually accompanied by a sustained elevation in temperature of one to two degrees F. and that a temperature of 99° to 99.4° F. was not infrequent during remissions. *Positive Wassermann, Kahn, Kline and Eagle tests had been obtained on repeated occasions.*

System Review. The patient had had almost constant bronchitis since 1938 and dyspnea as described above. Her appetite was always good. She had no nausea, vomiting, or stool abnormalities. She had had mild jaundice with exacerbations of weakness as mentioned above. After transfusions the urine was noticed to be very dark yellow but never red or black. She noticed tingling in bottom of feet only once and this was during the relapse of 1936. Her skin had gradually become darker since 1936 and appeared to be a sun tan.

Family History. Her mother was living and well. *Her father was a native of Greece.* The patient had an *identical twin sister* who had always been well but who had also been found to have *positive Wassermann, Kline, Kahn, and Eagle reactions.* No form of antisyphilitic therapy was ever given the twin sister who has not been available to us for study. The mother had remarried and later had three boys who were all living and well.

Marital History. She had been married 11 years and had one son 10 years old who was apparently normal. She had had several miscarriages but only one since 1934 which was in 1939 during a severe relapse of anemia.

Menstrual History. Her menstrual periods began at 13 years of age, occurred at 28 day intervals, and were normal in amount, lasting from three to four days except during periods of severe anemia, at which time the amount would be scanty.

Drugs. She had had numerous courses of intramuscular injections of liver, iron by mouth, aspirin for arthritis and various placebos. No drugs had been taken without the advice of physicians. Several intensive courses of bismuth intramuscularly and iodides by mouth had been administered without noticeable improvement during the course of her illness.

Physical Examination. On physical examination she had the appearance of a

person about 40 years of age. Temperature was 99.1° F. The pulse was 76 and respiration normal. Blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. The positive findings were confined to *splenomegaly, hepatomegaly,* and a *bronzing of the skin.* The spleen was palpable in the left side of the abdomen, moved on respiration, and extended 9 cm. below the left costal margin. The upper border of hepatic dullness began at the level of the fifth rib in the nipple line and extended inferiorly 13 cm. The lower edge was palpable and smooth. The bronzing of the skin involved the *entire body* and was similar in intensity to a good sun tan. All of the reflexes were physiological. Lymphadenopathy was confined to enlargement of the right submaxillary lymph node which was 1 cm. in diameter.

Laboratory Findings. Erythrocytes—3,780,000 per cu. mm. (Erythrocyte count was impossible with Hayem's diluting fluid because of marked clumping of cells. A slight amount was present when normal saline was used.) Hemoglobin—12 grams (Photoelectric). Leukocyte count—12,250. Differential: Mature segmented, 51 per cent; bands, 14 per cent; juveniles, 1 per cent; myelocytes, 2 per cent; plasma cells, 1 per cent; eosinophiles, 10 per cent; lymphocytes, 10 per cent; monocytes, 10 per cent; basophiles, 1 per cent.

A study of the blood film revealed numerous platelets, a moderate variation in the size of red cells, an occasional one being macrocytic, but most of the larger ones were normocytic with a considerable number of microcytic and well stained cells suggesting a possible spherocytosis.

Platelet count, 300,000 to 400,000; color index, 1.05; volume of packed cells, 37 per cent; volume index, 1.24; reticulocytes, 4.5 per cent; Price-Jones curve, average cell diameter 7.4 μ; icterus index, 5.0; van den Bergh, indirect, bilirubin content low. Kahn, 2+ to 3+ in various laboratories. Wassermann negative to 2+ in various laboratories. Fragility test: Patient—Hemolysis began at .46 per cent and was complete at .36 per cent NaCl solution. Control—Hemolysis began at .44 per cent and was complete at .34 per cent NaCl solution. Coagulation time five minutes. Donath-Landsteiner reaction negative. Heterophile agglutination positive through 1:8 dilution. Formol-gel reaction positive. Sedimentation rate (Wintrobe tube) 60 mm. in one hour.

As the red cells settled macroscopic clumping occurred. Gross clumping of the erythrocytes occurred within three to five minutes after being put in oxalate and citrate anticoagulants. No filaria were found in examinations of the peripheral blood at night. Her blood belonged to group O. For detailed results of crossmatching with various group O bloods see chart 1. If the clot was left in the serum for 12 hours no clumping occurred in the preparations of patient's serum and donor's cells and much less clumping occurred in the mixtures of the patient's cells with the patient's serum. When the clot remained in the serum for 24 to 36 hours very little to no clumping occurred in the preparations of patient's serum and patient's cells at room, ice box or body temperature, thereby indicating the absorbability of these auto-agglutinins.

Total protein (serum) 9.14 grams per 100 c.c.; albumin 3.78 grams per 100 c.c.; globulin 5.36 grams per 100 c.c.; A–G ratio 0.7 to 1. Spectroscopic examination of blood revealed no abnormal absorption bands.

Urine analysis: Albumin, negative; sugar, negative; acetone, negative; microscopic: occasional hyaline cast. Concentration test: concentrated to 1.020. Urea clearance, 103 per cent. Urobilinogen, not increased. Spectroscopic examination gave no abnormal bands.

Roentgenograms: Chest showed no abnormal findings. Skull and hands were negative for findings suggestive of Mediterranean anemia or multiple myeloma.

A skin biopsy was done and was negative for hemosiderin.

An hereditary anemia of the Mediterranean type seemed unlikely as the patient was so old when the erythroblastic crises developed and the bone changes characteristic

CHART I

Effects of Temperature on Cell Mixtures

	Room Temperature				
	30 Minutes	1 Hour	1½ Hours	2 Hours	12 Hours
Patient's serum with donor's* cells**	Negative	Negative	Occasional small clump, remainder of cells separate	Same as 1½ hours	Same as 1½ hours
Donor's serum with patient's cells**	Negative	Negative	Negative	Negative	Negative
Patient's serum with patient's cells**	Slight generalized clumping	Definite clumping	Definite clumping	Marked clumping	Marked clumping with fewer cells
Ice Box—42° F.					
Patient's serum with donor's cells**	Negative	Very occ. small clump. Remainder of cells well separated	Same as 1 hr.	Same as 1 hr.	Same as 1 hr. Slight decrease in number of cells
Donor's serum with patient's cells**	Negative	Negative	Negative	Negative	Negative
Patient's serum with patient's cells**	Some generalized clumping, slightly more than at room temperature	Definite clumping	Marked clumping	Marked clumping	Marked clumping but few cells present
Incubation—98° F.					
Patient's serum with donor's cells**	Negative	Tendency of some cells to group but not crowd together	Same tendency. More marked	Same as 1½ hours.	Occasional definite clumping with remainder of cells drifting
Donor's serum with patient's cells**	Negative	Negative	Negative	Negative	Negative
Patient's serum with patient's cells**	Slight tendency to clumping	Few small clumps	Marked amount of clumping	Definite clumping	Definite clumping. Fewer cells present. About same as 42° F.

* Donor is any group O used.
** Cell suspension of 6 drops of whole blood to 5 c.c. of normal saline.

of this condition were not present. Abnormal auto-hemolysins due to congenital syphilis were considered but thought unlikely because former courses of antisyphilitic treatment had not proved beneficial. In addition her mother had always been well, had had no miscarriages, and had borne three normal children, now living and well, by a second husband. Furthermore the Donath-Landsteiner reaction was negative.

The presence of an enlarged liver and spleen accompanied by an anemia characterized by exacerbations and remissions, with varying degrees of reticulocytosis in an individual having a twin sister with the same type of serological reactions to the syphilitic antigen seemed to indicate a diagnosis of atypical familial hemolytic icterus in remission and splenectomy was considered. The positive serologic reaction was regarded as that which might accompany any condition having marked reticulo-endothelial proliferation, regardless of the etiology, as seen in malaria, infectious mononucleosis, etc.

Course. The erythrocyte count began to decrease steadily. On January 19 it was 3,600,000 with 6 per cent reticulocytes; on the 20th 3,450,000 with 6 per cent reticulocytes, and on the 21st, 3,300,000 with 6 per cent reticulocytes. An impending relapse was feared and splenectomy was performed on January 23, 1940, without operative difficulties or complications. Red cell counts before, during, and after splenectomy were constant. The spleen weighed 617 grams, was without perisplenic adhesions, and possessed a red, firm cut surface with prominent fibrous septa. On microscopic study the essential features were confined to an extensive and marked hyperplasia of the reticulum and lymphoid elements with some increase in fibrous tissue among the reticular elements and marked engorgement of the sinusoids with red cells. On January 25 the red cell count rose to 3,920,000 with 8 per cent reticulocytes. Bronchopneumonia developed in the left lower lobe and was treated with 15 grains of sulfapyridine each four hours. Twenty hours after the onset of sulfapyridine therapy the red cell count was found to be 1,900,000 and the reticulocyte count 9 per cent. The drug was discontinued, and on January 27 the red cell count was 2,470,000 with 9 per cent reticulocytes.

A transfusion with whole blood was not attempted because of the severe reactions that had always followed these and the renal failure that had accompanied well matched blood on former occasions. The bronchopneumonia gradually improved and the red cell count remained about 2,000,000 until February 14, when it rose to 2,600,000 per cu. mm. Reticulocytes varied from 10 to 20 per cent during this time. From one to two normoblasts per 100 white cells were present. The leukocyte count remained about 10,000 per cu. mm. with immaturity to the myelocytic stage in some of the cells. *Repeated blood Kahn and Wassermann reactions were negative two weeks after splenectomy.* The disappearance of the positive Kahn reaction following splenectomy seemed further to substantiate the probability of previous false positive tests from reticuloendothelial proliferation, regardless of the etiology.

The site of the operative lesion healed without complications. The red cells were slow to return to higher levels but by March 4 had reached 3,000,000 per cu. mm. and the patient was allowed to return home. During May the red cells reached 3,500,000 per cu. mm. and the patient was without complaints.

In June while in her summer home in Maine, a relapse occurred with an erythroblastic crisis, and she returned to the Emory University Hospital. The red cell count fell to 1,700,000, reticulocytes rose to 45 per cent and 100 nucleated red cells were present to each 100 leukocytes. The blood serum and urine were negative for hematoporphyrin or other abnormal absorption bands by spectroscopic studies. The Wassermann and Kahn reactions continued negative. At this time the icterus index was 18, the bilirubin was 3.2 mg. per cent with an indirect Van den Bergh reaction, and the urobilinogen content of the urine slightly increased. Serum protein studies showed a total protein of 9.48 grams, albumin of 4.15 grams and globulin of 5.33 grams per 100 c.c. Antisyphilitic therapy in the form of potassium iodide and weekly injections of bismuth was instituted for several weeks without improvement. As a last desperate therapeutic possibility 10 grams of gum acacia were administered intravenously as a 6 per cent solution in normal saline in an attempt to lower the blood proteins, particularly the globulin portion. Serum protein studies taken three days

later revealed the lowest protein values found during the entire period the patient was under observation. The serum albumin was 3.75 gm., and globulin 4.00 gm., with a total protein value of 7.75 gm. (chart 2). The Greenberg method of determining serum proteins was used and the total protein values checked by means of the falling drop densiometer.

Her final relapse, in the form of an erythroblastic crisis, continued with the degree of anemia becoming more severe and without a detectable decrease in the titer of the auto-agglutinins. The red cells fell to 1,200,000 per cu. mm. with 58 per cent reticulocytes. Air hunger became marked and was partially relieved for a short time by the use of an oxygen tent. Five hundred c.c. of citrated blood of Group O which showed the best preparations when "cross-matched" with the patient were given slowly without reaction or improvement. The erythrocyte count dropped to 900,000, air hunger became marked, and a terminal coma followed.

Postmortem Examination. Only a small incision of the abdomen was made, since consent for a complete examination could not be obtained. The liver was large, weighing approximately 2000 grams and extending 8 cm. below the costal margin in the nipple line. The surface was smooth and on cut section pale and slightly greasy to palpation. There was no abdominal lymphadenopathy. The kidneys were pal-

CHART II

Date	Total Serum Protein	Albumin	Globulin	A-G Ratio
2–16–40	9.14 grams	3.78 grams	5.36 grams	1 : 1.4
7–25–40	9.48 grams	4.15 grams	5.33 grams	1 : 1.28
8– 9–40	10.66 grams	4.71 grams	5.95 grams	1 : 1.26
8–11–40	10 grams of acacia as 10 per cent solution in normal saline.			
8–14–40	7.75 grams	3.75 grams	4.00 grams	1 : 1.06

pated and normal in size. No abnormalities of the abdominal cavity were made out by palpation. The thoracic cavity was not entered.

On microscopic examination the kidneys were normal. There was no evidence of vascular disease, glomerulonephritis, or plugging of the tubules with hemoglobin crystals. The epithelial cells of the convoluted tubules contained a small amount of granular light yellow pigment.

Study of the liver revealed a marked generalized atrophy of the hepatic cells with a small amount of fatty change. *A single localized lesion* having epithelioid cells, giant cells, and a small amount of caseation necrosis was found. This resembled a miliary tubercle but acid fast stains did not reveal organisms. Silver stains by the method of Levaditi were negative for treponemata. Some of the liver triads showed a moderate increase in fibrous tissue with a marked round cell infiltration. Very small areas of fine fibrous tissue which penetrated to some extent among the surrounding hepatic cells were scattered throughout all liver sections studied. The polygonal cells immediately adjoining these areas were small, shrunken, and occasionally fragmented. Several areas consisting largely of plasma cells and lymphocytes were located in the subcapsular areas. No endarteritis could be demonstrated. The reticulo-endothelial cells of Kupffer were increased in number, and possibly responsible for the hepatomegaly since the polygonal cells appeared small and atrophic. The generalized atrophy of the hepatic cells could be secondary to the long standing anoxemia accompanying the anemic state rather than to a specific disease process. The areas of fibrous tissue, the chronic inflammatory cells, and the small granulomatous area were considered to be evidence of a chronic infection. Sections of both adrenals were normal.

Discussion

Auto-agglutination. The agglutination observed in this case was not that of pseudo-agglutination of the type observed in the hyperglobulinemia sometimes accompanying multiple myeloma, because these agglutinins were absorbed when the clot containing the red cells was left in the serum for six to 12 hours, or when the red cells of a citrated suspension of whole blood were allowed to remain in the plasma from four to eight hours. These agglutinins were not stronger at body temperatures, but on the contrary, slightly weaker; they resisted considerable dilution as demonstrated by the clumping occurring in the red cell counting pipette after undergoing a dilution of 200 times, and gave no indication of specificity in determining blood groups or subgroups. The auto-agglutination first observed by Reimann [3] in multiple myeloma and later by Bonniger [5] and Magnus-Levy [7] was apparently pseudo-agglutination which gave a rouleaux formation that could be broken up by agitation and was not accompanied by subsequent destruction and disintegration of the erythrocytes.

These atypical agglutinins resemble iso-agglutinins in their capacity for absorption, are little affected by temperature changes and stand considerable dilution, but are unlike iso-agglutinins in that no specific blood group is indicated and the patient's own serum acts strongly on the patient's own cells to bring about agglutination and fragmentation and a subsequent slow hemolysis.

These agglutinins conform more nearly to those classified as auto-agglutinins since they are absorbed, tolerate considerable dilution, and indicate no specific blood group or subgroup. Cold agglutinins are active at low temperature and belong to the group of auto-agglutinins. Stewart and Harvey [20] reported a case of hereditary auto-agglutination in which the cold agglutinins were demonstrated in mother and daughter. Wiener [21] considers the presence of non-specific auto-agglutinins as "a normal physiological phenomenon which is present in many animal sera with the titer being greatly increased in certain pathological conditions." This is said by some workers in hematology and immunology to be the basis of the hemolysis occurring in the Donath-Landsteiner test for paroxysmal cold hemoglobinuria, a condition most often associated with syphilis and usually responding to antisyphilitic therapy. McCombs [22] and Boxwell,[23] in separate studies, reviewed the cases reported in the literature having auto-hemagglutination. Many of them are clear cut instances of cold auto-agglutination. Other conditions cited as having high titers of auto-agglutinins are syphilitic cirrhosis of the liver, hemolytic icterus, Raynaud's vascular disease, trypanosomiasis, unexplained severe anemias, and obscure instances of no demonstrable disease.

Hyperglobulinemia. Protein values are rarely determined except in conditions of edema when hypoproteinemia is suspected. Hyperproteinemia has been observed mainly in chronic infections such as lymphopathia venereum, granuloma inguinale, chronic tuberculosis, leprosy, sarcoid of Boeck, syphilis, trypanosomiasis, filariasis, occasionally in rheumatoid arthritis, malaria, and in the neoplastic conditions of multiple myeloma, leukemia, lymphosarcoma, and malignant kidney tumors.

In this case protein determinations were carried out because of (1) the clumping of the erythrocytes in the red cell pipettes and sedimentation tubes; (2) the difficulty encountered in cross matching for transfusions; and (3) the serological reactions. Total serum and plasma protein determinations revealed

values of from 9 to 10 grams per 100 c.c., the total increase being caused mainly by elevation of the globulin protein to 5–6 grams per 100 c.c., and an accompanying reversal in the albumin-globulin ratio (chart 2). Except for very rare instances hyperproteinemia is caused by an increase in the globulin fraction above the normal limits of 2.5 to 3.0 grams per cent, thereby causing a reversal of the albumin-globulin ratio, since the albumin content remains normal.

The association of agglutinins with the plasma protein, particularly with one of the globulin fractions, has been indicated by many workers in immunology. Therefore, some type of chronic infection was suspected and searched for in this case, mainly on the basis of increased titer of non-specific auto-agglutinins which may have become elevated along with the production of specific antibodies during the development of immunity to the infection. This could be similar to the cold hemolysins found in rare instances of congenital syphilis, which produce the clinical syndrome of paroxysmal cold hemoglobinuria and give the Donath-Landsteiner phenomenon.

Bing and Plum [24] described an increase in plasma cells and reticulo-endothelial cells in and outside the bone marrow as the consistent pathological feature of hyperglobulinemia. Hyperglobulinemia is not a consistent feature of splenomegaly, even though it has often been observed in chronic infections associated with splenomegaly. Tertiary syphilis with splenomegaly and without alterations in the serum proteins have been observed by the writers. No significant protein changes followed splenectomy in this patient. The site of globulin formation has not been definitely established. Whether it be in the bone marrow, liver, or spleen, apparently the ubiquitous reticulo-endothelial system, if it is concerned with globulin formation, is capable of producing increased globulin levels in conjunction with the production of specific antibodies.

Positive Serological Studies. The behavior of the serologic reactions to various syphilitic antigens is sufficiently atypical to suggest the possibility of false positive reactions. However, inadequate courses of therapy with potassium iodide and bismuth could account for the doubtful to weakly positive serological reactions before splenectomy. The negative serological reactions following splenectomy are difficult to interpret unless this supports the contention that the reticulo-endothelium of the spleen plays a prominent rôle in the production of antibodies.

Use of Gum Acacia. The intravenous administration of gum acacia solution was a last desperate therapeutic effort as all others had been exhausted without success. This was done on the basis of the work of Yuile and Knutti [25] who, by the intravenous use of gum acacia in dogs, reduced the level of blood proteins, the globulin and fibrinogen portions being affected to a greater extent than was the albumin. The procedure was considered safe since the animals used by these workers remained in a satisfactory clinical condition, and acacia has been given on numerous occasions without untoward effects in instances of severe shock from hemorrhage. One injection of 10 grams as a 6 per cent solution in normal saline was given, with a decrease in the total blood protein to 7.75 grams. A greater decrease occurred in globulin than albumin with a subsequent lowering of the reversed albumin-globulin ratio (chart 2). Additional quantities of acacia were not given even though the globulin level had been lowered, mainly because it produced no abatement of the hemolytic crisis.

Diagnostic Possibilities. The clinical features in conjunction with the limited autopsy findings do not permit a clear unequivocal diagnosis. The most likely possibilities would include atypical chronic hemolytic anemia with auto-agglutination and hemolysis secondary to a chronic infection. The exact status of syphilis as the etiological agent cannot definitely be determined. The mother is said to have always been in good health, never had antisyphilitic treatment, no miscarriages, and to have had three normal boys by her second husband. However, the patient and her twin sister had positive serological reactions with various types of syphilitic antigens. The sister had always been well and the patient failed to respond to numerous courses of anti-syphilitic treatment during her five year period of illness. There is a possibility of an acquired syphilis in the patient as well as in her twin sister but from the history this appears unlikely. An enlarged liver with apparent atrophy of the individual cells, a granulomatous area of almost macroscopic size, and a slight degree of fine fibrosis in scattered areas seem to indicate a chronic infection, whether it be caused by an obscure unrecognized agent or an atypical reaction to syphilis.

An atypical type of familial hemolytic icterus should be considered. Little was known about the paternal side of the family except that the father was a native of Greece. The granulomatous areas present in the liver at autopsy were not typical of familial hemolytic icterus, nor was the fragility test positive. Furthermore, splenectomy did not effect a cure.

Mediterranean anemia in an adult with repeated erythroblastic crises is quite rare. The Grecian ancestry supports this possibility, but this is unlikely in view of the patient's age, lack of bone rarefaction in roentgenographic studies, and the autopsy findings.

No doubt one could apply the label of "acquired hemolytic anemia" to such a syndrome as seen in this patient, but this unsatisfactory designation is hardly adequate for scientific purposes. Moreover patients with the above disease do not show the auto-agglutination and hyperglobulinemia.

Conclusions

1. There is reported a case of atypical hemolytic anemia with auto-agglutinins and hemolysins associated with or caused by hyperglobulinemia.
2. No syndrome of hemolytic anemia with strong auto-agglutinins and hemolysins accompanied by hyperglobulinemia could be found in the medical literature.
3. Positive serological tests for syphilis, a microscopic granulomatous area in a liver section taken at autopsy along with generalized atrophy of the hepatic cords, and some irregular areas of fibrous tissue with round cell infiltration are presented as strongly indicative of a chronic infection, possibly syphilis.
4. The possible association of hyperglobulinemia with an increased titer of normal non-specific auto-agglutinins as the result of chronic infection, perhaps an atypical manifestation of syphilis, is discussed.

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THE CONTROL OF MASSIVE PULMONARY HEMORRHAGE BY PNEUMOPERITONEUM *

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Artificial pneumoperitoneum has become a valuable addition to the armamentarium of the phthisiologist in the treatment of selected cases of pulmonary tuberculosis.[1] The safety of inducing and maintaining a pneumoperitoneum, particularly from the pathological aspect, appears well established. Reports of repeated studies on autopsy material stress the fact that there are no changes in the abdominal viscera which can be attributed to the air introduced into the peritoneal space.[2]

Although uncontrollable hemorrhage from the lungs is considered an indication for this type of therapy, there is no mention in the literature of a case treated in this manner. It is apparent, however, that pneumoperitoneum has been successfully employed to control repeated small hemoptyses. The following is a case in which pneumoperitoneum was used for massive pulmonary hemorrhage, and in which the procedure proved dramatically effective.

Case Report

J. W., a white male, aged 25 years, was admitted to the St. Francis Hospital with a history of having coughed up about one teacupful of bright red blood the previous day. He had contracted an upper respiratory infection one week prior to admission and had expectorated blood-tinged sputum frequently. A history of recurrent pneumonias and several attacks of pleurisy affecting the left side of the chest was obtained. The first pneumonia occurred in 1936 and involved both lungs. Subsequently, the patient developed a persistent, productive cough. His condition was studied at the Chevalier Jackson Clinic in Philadelphia where numerous bronchoscopies were done, and a diagnosis of bronchiectasis affecting the bases of both lungs was reached.

In the early part of 1939, the patient suffered a second attack of pneumonia which involved the left lung and was accompanied by a marked pleuritis. In the spring of that year, he was hospitalized for one week because of repeated hemoptyses. Upon recovery, he was advised to reside in a more equable climate, such as that found in Florida.

Except for the diseases common to childhood, the patient had been free of any major illness until 1936. Although he had developed chest colds frequently, he denied having any symptoms of sinus trouble. There was no history of familial cancer, lung disease, or any known contact with tuberculosis. The patient's wife was receiving treatment for a severe Vincent's angina at the time his present illness began, but there was no evidence that the spirochetal infection had been transmitted to or from the patient.

On August 29, 1941, the day of admission to the hospital for his present condition, the patient appeared pale, weak, apprehensive, and acutely ill with temperature of 99° F., pulse 104, respiration 24, and blood pressure of 118 mm. Hg systolic and 74 mm. diastolic. He had a frequent, harsh cough and expectorated a scant amount of blood-streaked sputum. Physical examination revealed the following positive findings: pale conjunctivae and fundi, granular and inflamed pharyngeal mucous membranes, slight postnasal drip, moderate-sized blood clot in the posterior nasopharynx, cold, moist

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skin of poor texture, and cyanotic fingernail beds. His chest was symmetrical in size and shape, and expanded evenly and equally in its upper part but lagged at the left base during respiration. There was a hyper-resonant note on percussion over the base of the right lung and dullness at the left base. Many sonorous and sibilant râles were heard over the right base, anteriorly and posteriorly, and to a lesser degree at the left base, where the breath sounds were diminished in intensity. Laboratory

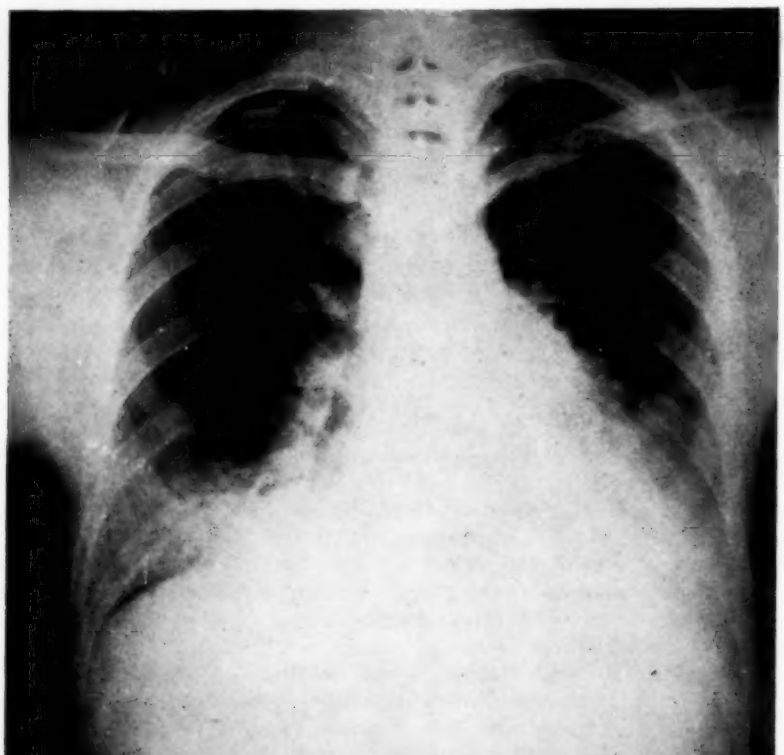

FIG. 1. Roentgenogram of chest before treatment.

study showed the following: red blood cells 4.5, hemoglobin 13.68 grams (86 per cent), white blood cells 16,000, polymorphonuclears 50 per cent, segmented 41 per cent, nonsegmented 9 per cent, and lymphocytes 50 per cent; clotting time 2 min. 50 sec., and bleeding time 45 sec.

Treatment was directed primarily toward preventing further hemorrhage and replacing the blood loss. Oxygen was given for the anoxemia, and sedatives for the cough, restlessness, and apprehension. August 30, 1941, the patient suddenly coughed up approximately 675 c.c. fresh blood. Two days later, September 1, 1941, he was

awakened by a spasm of coughing and expectorated 200 c.c. blood. That afternoon he had another hemorrhage of 200 c.c. In the evening his temperature rose to 102.6° F., pulse 125, and respiration 36. The laboratory examinations showed: red blood cells 3.6, hemoglobin 10.62 grams (67 per cent), white blood cells 22,300, polymorphonuclears 80 per cent, segmented 56 per cent, nonsegmented 21 per cent, juveniles 3 per cent, and lymphocytes 20. Roentgenograms of his chest showed a diffuse, mottled shadow in the right lower lobe, close to the cardiac border, which was suggestive of an acute pneumonitis, and also changes caused by the aspiration of blood. A dense shadow, triangular in outline, extended from the left hilum area downward and laterally into the left base, and appeared to be an atelectatic left lower lobe. The trachea was slightly displaced toward the left side (figure 1).

Although there was a difference of opinion regarding the site of the hemorrhages, it was considered probable that the bleeding originated in the left lung. However, in view of the history of recurrent pleurisy on the left side, the possibility of obtaining a satisfactory collapse of the bleeding area in that lung by artificial pneumothorax seemed very unlikely. Bronchoscopy was considered inadvisable at this time because of the patient's grave condition and the recent bleeding. Sulfathiazole, coagulants, and a transfusion of 300 c.c. citrated blood were administered. The following day, September 2, 1941, the patient was given another transfusion of 300 c.c. citrated blood, and also 10 per cent dextrose in Ringer's solution. On September 3, 1941, the patient experienced a marked reaction to a transfusion of 400 c.c. citrated blood in the form of a severe chill and a sharp rise of temperature to 106° F. The therapy now included calcium, parathyroid extract, vitamins C, D, and K, and thromboplastin. The sulfathiazole concentration in the blood had now reached 6 mg. per cent.

On September 4, 1941, he had two hemorrhages of 150 c.c., and 90 c.c. respectively. Blood culture was negative for organisms; the red blood cell count fell to 3.5, the hemoglobin to 10 grams (63 per cent). Sputum smear and culture were negative for acid-fast bacilli, but showed many Gram-negative cocci and bacilli, *N. catarrhalis,* and *Staphylococcus albus.* No spirochetes were reported. The patient was placed within an oxygen tent and frequent but small amounts of whole blood were given daily by direct transfusion. Citrated blood was replaced by whole blood as the former seemed to increase the patient's tendency to hemorrhage. However, on September 7, 1941, another hemorrhage of 90 c.c. blood occurred. A roentgenogram of the chest revealed some clearing of the mottled shadow at the base of the right lung, and increased aeration of the atelectatic left lower lobe.

During the next day, the patient experienced three hemorrhages, 1500 c.c., 150 c.c., and 90 c.c., respectively. As mechanical compression of the bleeding area appeared to be the only practicable method of preventing further hemorrhage, artificial pneumoperitoneum was induced. The patient, being too dyspneic to lie flat upon his back, was placed in the Fowler position for this procedure. His bladder was emptied, and 1000 c.c. air were injected intraabdominally at a point two fingers' breadth above and to the left of the umbilicus. The intraperitoneal pressure was raised to plus 7 mm. water. A roentgenogram of the chest showed a one inch separation of the diaphragm from the abdominal organs, but there was no apparent elevation of the diaphragm as regards rib level. The patient's temperature had risen to 102° F., the red blood cells had fallen to 3.2, the hemoglobin to 9.37 grams (59 per cent), and the color index to 0.92. The white cell count was 13,800, polymorphonuclears 59 per cent, segmented 45 per cent, nonsegmented 13 per cent, juveniles 1 per cent, and lymphocytes 41 per cent.

For several days there was slight fever with an evening rise to 100° F. After freedom from bleeding for seven days, the patient, on September 16, 1941, had three hemorrhages of 25 c.c., 75 c.c., and 25 c.c. fresh blood. That day, a pneumoperitoneum refill was given—1000 c.c. air with a final pressure of plus 8 mm. water. The

following day, the patient coughed up about 10 c.c. bright red blood. On September 18, 1941, a 300 c.c. hemorrhage occurred.

At this time it was decided that pneumoperitoneum refills would be given every second day in order to obtain a maximum elevation of the diaphragm. At each refill the amount of air administered would be increased until the intraperitoneal pressure reached the highest point that the patient could tolerate without too much discomfort.

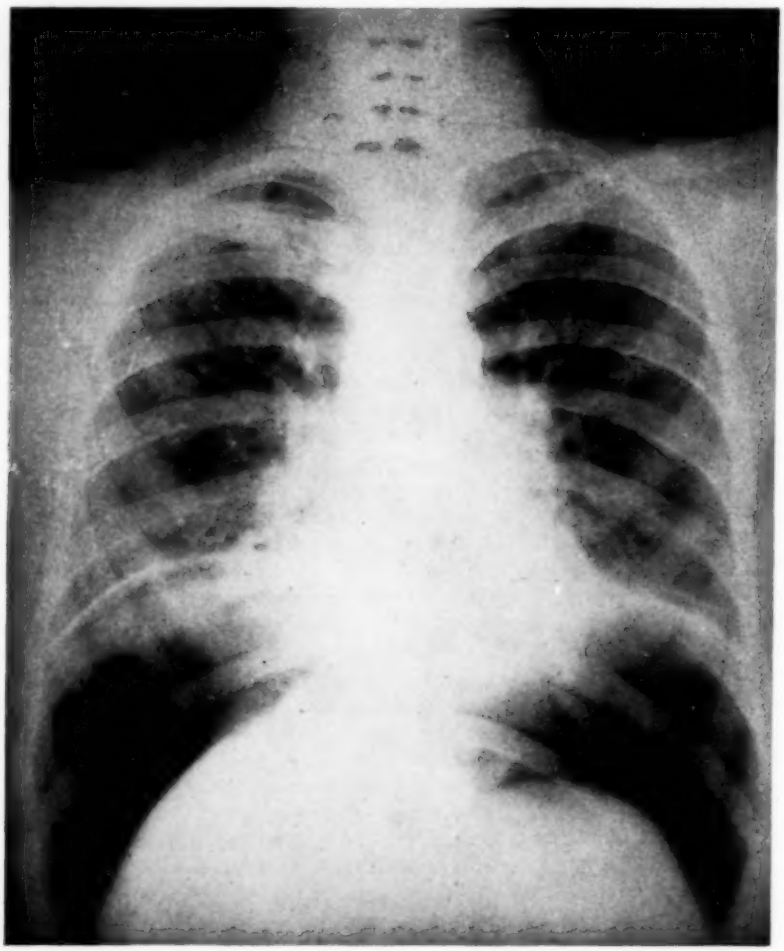

FIG. 2. Roentgenogram of chest after pneumoperitoneum was established.

It was also agreed that a temporary phrenic nerve crush would be performed to supplement the action of the pneumoperitoneum, if the pneumoperitoneum, itself, failed to control the bleeding.

Despite this régime, the patient bled twice on September 21, 1941, losing 1100 c.c. and 150 c.c. blood. Another hemorrhage of 850 c.c. took place on September 24, 1941. It was evident that the air introduced into the peritoneal cavity was being absorbed very rapidly. Amounts of air had been administered every other day to raise the intraperitoneal pressure to plus 14 mm.–16 mm. water. Nevertheless, at each refill

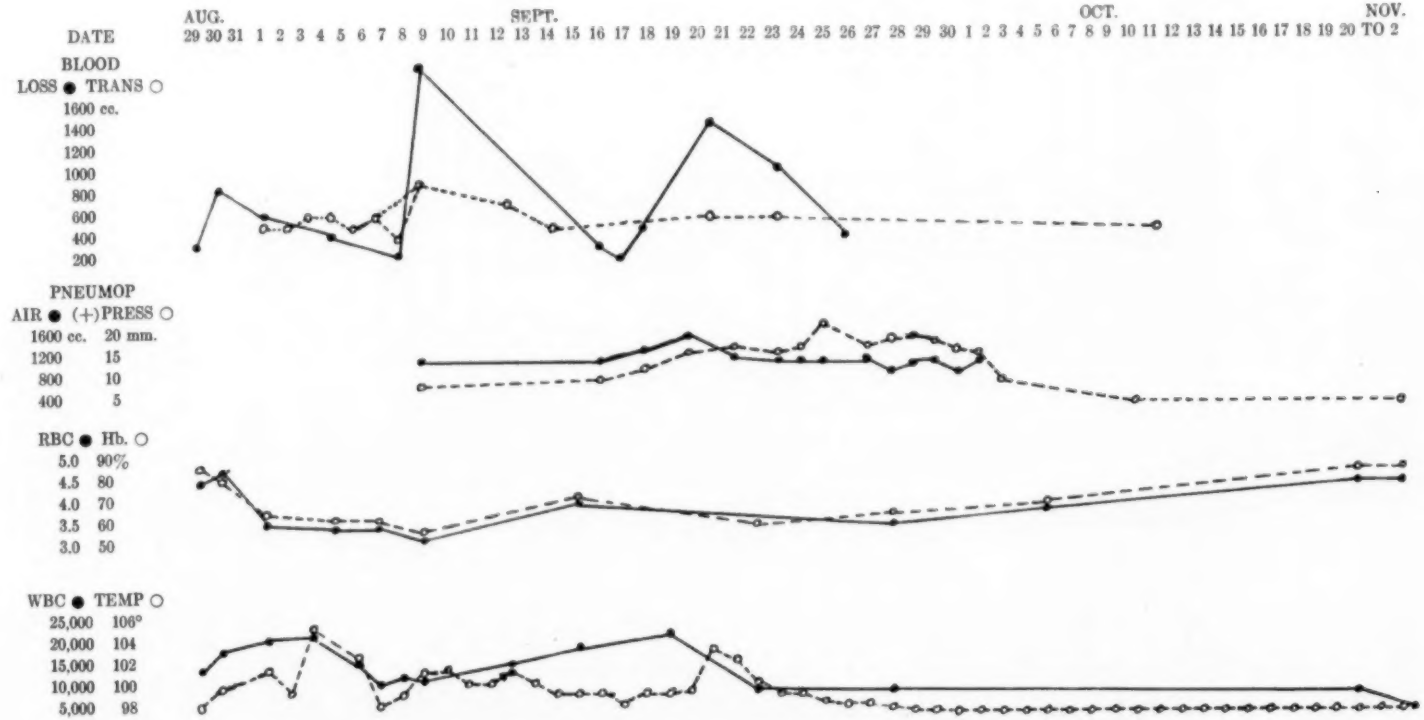

FIG. 3. Chart summarizing data as to hemorrhages and results of treatment.

the initial manometer reading was found to be less than plus 7 mm. water. Consequently, it was necessary to institute a course of daily pneumoperitoneum refills. Each day approximately 1000 c.c. air were injected to maintain the intraperitoneal pressure at plus 16 mm. to plus 18 mm. water.

As the patient's sputum had been free of blood for three days, and as there was considerable discomfort due to the marked abdominal distention, which was not relieved by changes in position, the refill for September 27, 1941 was omitted. That night he awoke and coughed up frothy mucopurulent sputum containing about 250 c.c. fresh blood. Daily pneumoperitoneum refills were resumed and continued for the next seven days. There were no further hemorrhages, and the sputum became clear of any trace of blood within a few days. The patient began to expectorate foul-smelling material copiously. At this stage, a chest roentgenogram showed further clearing at the base of the right lung, and increased aeration of the left lower lobe. The diaphragm was elevated to the level of the eighth rib on the right side and to the eighth intercostal space on the left (figure 2). This was an appreciable rise as compared to previous films of the chest taken at the same phase of respiration.

Beginning on October 4, 1941, 100 c.c. to 300 c.c. air were aspirated from the peritoneum at intervals, reducing the intraperitoneal pressure to plus 4 mm. water. The air remaining in the peritoneal space was left to be absorbed spontaneously.

Subsequently, the patient's recovery was uneventful. He had lost 18 pounds during his acute illness but regained eight pounds prior to his discharge from the hospital. He was allowed out of bed for the first time on October 9, 1941. He was referred to the Chevalier Jackson Clinic on November 2, 1941 for further study in preparation for lobectomy. At the time of discharge his temperature had been normal for one month. Laboratory study showed the following: red blood cells 4.5, hemoglobin 13.68 grams (86 per cent), C. I. 0.95, and white blood cells 5000. His final chest film revealed the diaphragm elevated to the level of the lower border of the ninth rib, complete resolution of the shadow at the base of the right lung, and a well aerated left lower lobe. A partial pneumoperitoneum was still present, and the intraperitoneal pressure was equal to plus 3 mm. water.

In all, 14 pneumoperitoneum refills were administered, making a total of approximately 14,500 c.c. air. Despite daily refills of about 1000 c.c. air, no complications occurred. The only untoward effect of maintaining the exceedingly high intraperitoneal pressure consisted of moderate discomfort due to the marked abdominal distention, which was usually relieved by elevating the foot of the patient's bed. There could be no doubt that the pneumoperitoneum was effective in controlling the pulmonary hemorrhages. From the date of admission, the patient had 19 hemorrhages, 16 of them massive, and had lost over 6000 c.c. blood within the period of less than 30 days. In that period, he received 13 transfusions, making a total of approximately 5000 c.c. blood (figure 3).

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1. Banyai, A. L.: Therapeutic pneumoperitoneum, Am. Rev. Tuberc., 1934, xxix, 603.
2. Fowler, W. O.: Pneumoperitoneum in the treatment of pulmonary tuberculosis, Am. Rev. Tuberc., 1941, xlix, 474–478.

EDITORIAL

ANTIBIOTIC SUBSTANCES PRODUCED BY MICROÖRGANISMS

MANY instances are known in which the presence and growth of one microörganism is antagonistic to the growth and multiplication of another species. One of the best examples of this action became known through the observation of Fleming [1] that colonies of a certain species of mould (*Penicillium notatum*) inhibited the growth of colonies of many species of bacteria in their vicinity. He showed that the inhibiting substance, which he named penicillin, was present in broth culture filtrates of the organism. He demonstrated that its action was selective and limited largely to Gram-positive organisms, particularly the pyogenic cocci. On the other hand it had little or no effect on Gram-negative organisms of the typhoid-colon group or on Pfeiffer's influenza bacillus. Isolation of the latter was facilitated by adding penicillin to the culture media in order to inhibit the growth of other organisms.

Fleming also reported that penicillin was nonirritant and nontoxic to animals, even in large doses, and suggested that it might be effective in treating infections due to organisms susceptible to its action. However, no active interest in its clinical use was aroused until Chain, Florey, et al.[2, 3] again demonstrated its lack of toxicity for mice and reported its successful use in a small series of human infections.

Another important contribution was made by Dubos [4, 5] who, by an ingenious method, isolated from soil a Gram-positive spore-bearing bacillus (later known as *Bacillus brevis*) which exerted a powerful bactericidal effect on many Gram-positive organisms, including pneumococci, hemolytic streptococci and staphylococci. The active substance was present in the culture medium after autolysis of the organisms. Administered intraperitoneally, it protected mice from large doses of virulent pneumococci similarly injected, and exhibited some curative effect. The active substance, to which the name tyrothricin was later given, was found to contain two active ingredients, tyrocidin and gramicidin, both polypeptids. The latter was much the more potent and important. In amounts as small as one microgram per c.c. it prevented growth of pneumococci in broth cultures, and from one to five micrograms, injected intraperitoneally, protected mice

[1] FLEMING, A.: The antibacterial action of cultures of a *Penicillium*, with special reference to their use in the isolation of *B. influenzae*, Brit. Jr. Exper. Path., 1929, x, 226.

[2] CHAIN, E., FLOREY, H. W., et al.: Penicillin as a chemotherapeutic agent, Lancet, 1940, ii, 226–228.

[3] ABRAHAM, E. P., CHAIN, E., et al.: Further observations on penicillin, Lancet, 1941, ii, 177.

[4] DUBOS, R. J.: Studies on a bactericidal agent extracted from a soil bacillus. I. Preparation of the agent. Its activity in vitro, Jr. Exper. Med., 1939, lxx, 1.

[5] DUBOS, R. J.: Studies on a bactericidal agent extracted from a soil bacillus. II. Protective effect of the bactericidal agent against experimental pneumococcus infections in mice, Jr. Exper. Med., 1939, lxx, 11.

from one million fatal doses of culture similarly administered. It was actively hemolytic, and in somewhat larger doses was highly toxic for these animals.

Tyrothricin has had a fairly extensive trial in cases of human infection, and it has been highly effective against pneumococcus and streptococcus infections (but only feebly so in staphylococcus infections) when applied locally to external wounds, ulcers or sinus tracts, to the mucosa of the nasopharynx, the bladder, or the pleura in empyema.[6, 7, 8] It was found to be too toxic for parenteral administration, however, and is ineffective by mouth. When given intravenously to animals with systemic infections it was practically inert. Its usefulness is therefore strictly limited to superficial infections in which it can be brought into direct contact with the microorganisms concerned.

The promising if restricted results obtained clinically by the use of gramicidin and particularly of penicillin [3] naturally stimulated a search for similar substances produced by other organisms, especially among the moulds. A number of such antibiotic principles have been demonstrated. Thus from species of *Actinomyces* three distinct substances have been obtained: actinomycetin (a polypeptid), streptothricin (an organic base), and actinomycin (a pigment). Fungi of the genus *Aspergillus* have contributed several. Among these are aspergillin, from *A. flavus;* fumagacin, from *A. fumagatus,* and clavacin (a lipoid) from *A. clavatus.* Gliotoxin was obtained from *Gliocladium fimbriatum,* and claviformin from *Penicillium claviforme.* Other antibiotics which differ from penicillin chemically and in their range of action have been isolated from cultures of *Penicillium notatum.*

These substances differ considerably from one another in their chemical characteristics, potency, range of action and toxicity. Some are active on bacterial species not affected by penicillin. Most of them are relatively ineffective on Gram-negative bacilli, but streptothricin is an exception in this respect. Most of them are more or less toxic for animals, some highly so. The more important of these antibiotics have been studied and compared by Waksman.[9, 10] None has yet been sufficiently studied to determine its clinical usefulness. There can be little doubt, however, that eventually some such products will be found which will supplement the many deficiencies of penicillin and possibly supplant it entirely.

Following the publications of Florey et al., interest has centered in penicillin, and clinical tests have been carried out as extensively as the scanty quantities available permitted. Their results have been confirmed and ex-

[6] HERRELL, W. E., and HEILMAN, D.: Experimental and clinical studies on gramicidin, Jr. Clin. Invest., 1941, xx, 583.

[7] RAMMELKAMP, C. H.: Use of tyrothricin in the treatment of infections, War Med., 1942, ii, 830.

[8] BORDLEY, J. E., CROWE, S. J., et al.: The local use of the sulfonamides, gramicidin (tyrothricin) and penicillin in otolaryngology, Ann. Otol., Rhin. and Laryng., 1942, li, 936.

[9] WAKSMAN, S. A., and WOODRUFF, H. B.: Selective bacteriostatic and bactericidal action of various substances of microbial origin, Jr. Bact., 1942, xliii, 9.

[10] WAKSMAN, S. A.: Nature and mode of action of antibiotic substances, Jr. Bact., 1943, xlv, 64.

tended by (among others) Herrell and associates, Rammelkamp and Keefer, and Florey and Florey. Finally Keefer and associates [11] have just reported the results of the treatment of 500 cases of various infections, carried out under the auspices of the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council. This report should be read carefully by everyone interested in the subject.

One of the most valuable properties of penicillin is its almost complete lack of toxicity, even when given intravenously in very large doses. Apparently penicillin will accomplish all or nearly all that can be done by the sulfonamides as well or better than they, with negligible chance of toxic reactions. It is highly effective against pneumococcus, hemolytic streptococcus and gonococcus infections, including those caused by strains which are resistant to sulfonamides. It is much superior to sulfonamides in the case of staphylococcus infections, although relatively large doses are required. Of 91 cases of *Staphylococcus aureus* sepsis, 60 per cent recovered or greatly improved,[11] in contrast with the average mortality in untreated cases of this type of about 85 per cent. There is reason to hope that it will be effective also in infections with the Gram-positive anaerobic bacilli.

In view of the great interest and perhaps rather uncritical enthusiasm which penicillin has aroused, it seems desirable to emphasize its defects and limitations as well as its remarkable therapeutic powers.

One of the most serious obstacles to the use of penicillin is the difficulty of preparing it in quantity and its high cost. Only minimal amounts are produced in the cultures, and it is so unstable that a substantial part is lost during its recovery and purification. Florey [3] in connection with his earlier preparations reported that the crude filtrate contained from one to two units per c.c., and that only one-third of this was recovered, so that 100 liters of culture were required to produce one gram of therapeutic material containing 40 to 50 units per mg. (50,000 units in all). One Oxford unit was defined as the minimum amount of penicillin which would completely inhibit the growth of a test strain of *Staphylococcus aureus* when dissolved in 50 c.c. of meat extract broth. Further purification yielded a product containing about 500 units per mg., but with additional loss in the yield. As the amount recommended for the treatment of a severe infection is about 120,000 units a day, and as administration may have to be continued for 7 to 14 days, it is obvious why the use of penicillin is still on a very restricted experimental basis and why it is still unobtainable for general civilian use.

The intensive efforts being made to improve the methods of production have doubtless increased the yield substantially, but Richards [12] has recently stated that one gram from 20 liters of culture would be exceptionally high. Merely to supply the expected needs of the armed forces is a herculean task which seems practically an impossibility unless a method of synthesizing

[11] Keefer, C. S., Blake, F. G., Marshall, E. K., Jr., Lockwood, J. S., and Wood, W. B.: Penicillin in the treatment of infections; Statement by the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council, Jr. Am. Med. Assoc., 1943, cxxii, 1217.

[12] Richards, A. N.: Penicillin. Statement released by the Committee on Medical Research, Jr. Am. Med. Assoc., 1943, cxxii, 235.

penicillin can be devised. Reports so far published give very little information as to its structure, but its apparent relative complexity and marked instability suggest that synthesis may prove a tedious and difficult task.

The administration of penicillin also offers some practical difficulties. The action of penicillin is largely bacteriostatic, only in part bactericidal, particularly on staphylococci. To be effective, the organisms must be kept continuously in contact with penicillin in adequate concentration (about 0.02 to 0.15 units per c.c.[13]) until recovery is complete. Penicillin is inert by mouth, and must be given by parenteral injection. When so given it is so rapidly excreted in the urine that, in order to maintain an effective concentration in the blood, it must be given by continuous intravenous drip or by intravenous or intramuscular injections repeated every two to four hours. Hobby et al. have reported that mice can be protected from pneumococcal and streptococcal infection by a single subcutaneous injection of an oil suspension of penicillin, and by the subcutaneous implantation of a single pellet mixed with cholesterol. It seems possible that some similar procedure might be devised for the treatment of human cases.

It is probable that penicillin will be effective in the treatment of meningococcus infections, as it acts strongly on this organism in vitro. As little if any penicillin enters the spinal fluid after intravenous injection, it is probable that intrathecal as well as intravenous injections will be required in cases of meningitis.

Penicillin-fast strains have been reported in the case of pneumococci, hemolytic streptococci and staphylococci. This resistance may develop either in vivo or in vitro, but it appeared only after protracted continuous exposure of the organisms to penicillin. Such strains, however, were found to have largely lost their virulence, and they continued to be sensitive to the sulfonamides.

Penicillin is definitely restricted in the range of its activities, and there are many organisms that are resistant. As far as present studies go, there is a close parallelism between its activities in vitro and in vivo. It has no action on *Streptococcus fecalis* and on some other strains of *Streptococcus viridans*. It had no effect, or only a very temporary one in 17 cases of subacute bacterial endocarditis in which it was tried. Like the sulfonamides, it seemed to cause temporary sterilization of the blood stream in a few cases.

Penicillin has been reported to be inactive in vitro and in some cases in vivo toward the Gram-negative bacilli of the colon, typhoid, *Salmonella* and dysentery groups, toward *Brucella*, the influenza bacillus, Friedländer's bacillus, *Proteus*, the pyocyaneus bacillus, the cholera vibrio and the tubercle bacillus.

In spite of these drawbacks, penicillin is a remedy of extraordinary value. The perfection of some method which would make possible its production on a large scale and at reasonable cost would be a therapeutic advance comparable in importance to the discovery of the sulfonamides.

[13] RAMMELKAMP, C. H., and KEEFER, C. S.: Penicillin; its antibacterial effect in whole blood and serum for the hemolytic streptococcus and *Staphylococcus aureus*, Jr. Clin. Invest., 1943, xxii, 649.

REVIEWS

The Addendum to the Chemistry of the Amino Acids and Proteins. Edited by CARL L. A. SCHMIDT, M.S., Ph.D., Professor of Biochemistry and Dean of the College of Pharmacy, University of California. 12 contributors. 1290 pages; 17 × 26 cm. Charles C. Thomas, Springfield, Ill. 1943. Price, $5.00.

This book, designed to bring the chemistry of the amino acids and proteins up to date in lieu of a completely revised second edition, serves its purpose very well. The added material, covering the period from 1937 to 1942, is arranged in chapters which follow the numbering of the parent volume for easy reference. There is a good bibliography. The addendum also appears as a supplement to the second edition of "The Chemistry of the Amino Acids and Proteins."

M. A. A.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Hypertension. By IRVINE H. PAGE, A.B., M.D. 80 pages; 19.5 × 13 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $1.50.

Handbook of Tropical Medicine. By ALFRED C. REED, M.D., and J. C. GEIGER, M.D. 188 pages; 17 × 11.5 cm. 1943. Stanford University Press, Stanford University, California. Price, $1.50.

Notes on Gas Gangrene. Prevention—Diagnosis—Treatment. By the War Wounds Committee of the Medical Research Council and the Committee of London Sector Pathologists. 28 pages; 24.5 × 15.5 cm. 1943. His Majesty's Stationery Office, London. Price, 6d. net. (Medical Research Council War Memorandum No. 2—Revised Second Edition.)

Kaiser Wakes the Doctors. By PAUL DE KRUIF. 158 pages; 21 × 14 cm. 1943. Harcourt, Brace and Company, 383 Madison Avenue, New York City. Price, $2.00.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,471 Fellows and Associates of the College on active military duty. Herewith are reported the names of 11 additional members, bringing the grand total to 1,482.

Samuel C. Arnett, Jr.
Roland W. Banks
Meyer Bloom
Mahlon H. Delp
George C. Griffith
Henry B. Gwynn
Tim J. Manson
Henry C. Rosenstiel
Lauren H. Smith
Albert M. Snell
Charles E. Thompson

New Life Member of the College

Dr. John Robert Van Atta, F.A.C.P., Albuquerque, N. M., has subscribed to Life Membership, and his initiation fee and Life Membership subscription have been added to the permanent Endowment Fund of the College.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Maxwell Finland, F.A.C.P., Boston, Mass.—2 bound volumes, "Collected Reprints";
Dr. James H. Hutton, F. A. C. P., Chicago, Ill.—"War Endocrinology."

Reprints

Dr. John D. Adcock (Associate), Ann Arbor, Mich.—4 reprints;
Dr. Otis L. Anderson, F.A.C.P., U. S. Public Health Service, Bethesda Station, Md.—4 reprints;
Dr. George E. Baker, F.A.C.P., Casper, Wyo.—2 reprints;
J. Edward Berk, F.A.C.P., Captain, (MRC), U. S. Army—1 reprint;
Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—2 reprints;
Edgar Durbin, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Jack D. Kirshbaum (Associate), Major, (MRC), U. S. Army—3 reprints;
Alfred L. Kruger (Associate), Captain, (MRC), U. S. Army—7 reprints;
Dr. Jerome A. Marks, F.A.C.P., New York, N. Y.—1 reprint;
Benjamin H. Neiman (Associate), Major, (MRC), U. S. Army—1 reprint;
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint;
Dr. Marjorie E. Reed, F.A.C.P., Plymouth, Pa.—1 reprint;
Eugen G. Reinartz, F.A.C.P., Brigadier General, (MC), U. S. Army—3 reprints;
Howard A. Rusk, F.A.C.P., Major, (MRC), U. S. Army—2 reprints;
Dr. Howard Wakefield, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Albert Weinstein, F.A.C.P., Nashville, Tenn.—1 reprint.

College Committees and Regents to Meet, November 19–20

The regular autumn meeting of the College Committees and of the Board of

Regents will be held at the College Headquarters, Philadelphia, Friday and Saturday, November 19–20, to transact the customary business of the College and to pass upon the credentials of candidates for Associateship and Fellowship. Proposals of candidates must be filed in the Executive Offices of the College thirty days in advance of action. The next succeeding meeting will be held in the late winter.

A. C. P. Postgraduate Course and Regional Meeting, Philadelphia

Postgraduate Course No. 3, "Special Medicine," in the series of courses offered by the College to its members during the autumn of 1943, will be held in various Philadelphia institutions during the two-week period, November 8–19. The program is unique in that it allots approximately one-half day to the consideration of each of several special fields of medicine and will be given in eleven different institutions in Philadelphia. The faculty consists of one hundred and three teachers, all recognized authorities in their special fields.

The concluding day, Friday, November 19, will be devoted to a Regional Meeting of the College for Pennsylvania, New Jersey, Delaware, and adjacent territory. The Regional Meeting program will consist of a morning program of clinical presentations at the Hospital of the University of Pennsylvania and of an afternoon scientific program of six papers by eminent authorities, Service and Civilian. In the evening there will be a cocktail party and dinner meeting at which will be represented in person or by envoy, the Surgeons General of the U. S. Army and U. S. Navy, and other distinguished medical men. Timely, short addresses will be given by the President of the College and others.

Dr. Ward Darley, F.A.C.P., Denver, Colo., has retired from private practice in order to accept a full-time teaching post as Associate Professor of Medicine at the University of Colorado School of Medicine.

Dr. Franklin H. Top (Associate), Director of the Division of Communicable Diseases and Epidemiology of the Detroit (Mich.) Department of Health, has been appointed also Medical Director of the Herman Kiefer Hospital, Detroit.

New Acting Governor for Maine

Owing to active military service in the U. S. Navy, Lieutenant Commander Eugene H. Drake, College Governor for Maine, has been granted leave of absence and Dr. Richard S. Hawkes of Portland, Maine, has been named the Acting Governor by the Executive Committee of the Board of Regents.

Dr. Carleton B. Peirce, F.A.C.P., Montreal, Can., has been appointed by the Governors of McGill University as Chairman of the Department of Radiology in the Faculty of Medicine as of June 1, 1943. Dr. Peirce for the past year has been on loan from the Royal Victoria Hospital and McGill University to the Royal Canadian Navy as the Consultant Radiologist for that Service, but at the same time he has been devoting as much time as possible to his responsibilities as Radiologist-in-Chief at the Hospital and to his teaching work at McGill University.

Dr. Carroll M. Pounders, F.A.C.P., Oklahoma City, Okla., has been appointed by the President of the Southern Medical Association as the Oklahoma representative on its Council.

Dr. Christopher G. Parnall, F.A.C.P., Medical Director of the Rochester (N. Y.) General Hospital, has been granted a leave of absence to serve as Director of a survey of twenty-six state operated mental hospitals, the survey being provided for under the Moreland Act. There will be six main divisions of study: "Studies and inquiries into admission and discharge procedures, personnel, professional care of patients, physical plans in the hospital structures, collection of funds for patient care, and administration." Dr. Parnall will be assisted by a staff of experts.

American Board of Pediatrics Examinations

The American Board of Pediatrics has announced its written examination locally under a monitor, February 4, 1944. Its oral examinations will be held in Philadelphia, March 25–26, and in San Francisco, May 6–7. C. A. Aldrich, M. D., Secretary, 707 Fullerton Ave., Chicago, Ill.

At the recent annual meeting of the Chicago Society of Internal Medicine, the following officers were elected for 1943–44: President, Dr. Italo F. Volini, F.A.C.P.; Vice-President, Dr. Howard Wakefield, F.A.C.P.; Secretary, Dr. Howard L. Alt.

Baylor University College of Medicine has moved its equipment from Dallas to Houston where it has set up temporary quarters for the future conduct of the School. The Jefferson Davis Hospital and the Hermann Hospital furnish clinical accommodations. Houston physicians are coöperating in the teaching. Eighty-four students are in the freshman class, but the upper classes are smaller. The School, while still in Dallas, had Army and Navy contracts, and it is said that all the Navy students who were in Dallas have been ordered to Houston. Dr. James A. Greene, F.A.C.P., formerly Associate Professor of Medicine at the State University of Iowa College of Medicine, has accepted an appointment as Professor and Chairman of the Department of Medicine and Dean of the clinical faculties.

Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, Dr. Virgil P. W. Sydenstricker, F.A.C.P., Augusta, Ga., and Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, are members of the faculty of a refresher course for practicing physicians that will be offered by the Medical College of the State of South Carolina at Charleston, November 3–4.

Dr. Everett K. Geer, F.A.C.P., St. Paul, Minn., addressed the 30th Annual Meeting of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Trudeau Society at Chicago, September 8–9, on the subject "Transient Infiltration of the Lung Parenchyma Associated with Eosinophilia."

Through the assistance of the Chinese Foundation, the Chinese Medical Journal, whose publication was suspended when the Japanese invaded Peking in December, 1941, has resumed publication on a quarterly basis in this country at P. O. Box 6096, Washington, D. C. It is said that printing and circulation facilities in Free China are inadequate, although the medical profession in China will still have its Chinese edition.

Dr. Charles Walter Clarke, F.A.C.P., Executive Director of the American Social Hygiene Association, New York City, has been named Clinical Professor of Public Health Practice at Harvard University.

Dr. James E. Paullin, F.A.C.P., President of the American College of Physicians and of the American Medical Association, addressed the Milwaukee County Medical Society, September 14; the Philadelphia County Medical Society and College of Physicians of Philadelphia, September 15; and the Michigan State Medical Society, September 22, at Detroit, on "The Responsibility of the Medical Profession in Post-war Planning."

Dr. Charles A. Doan, F.A.C.P., Professor of Medicine and Director of Medical Research, Ohio State University College of Medicine, Columbus, has been made President of the Ohio Public Health Association.

The State of Georgia has initiated annual registration of all licentiates of state examining boards. This began on September 1. No fees at present are required.

Some other states have long since initiated an annual registration. For instance, in Nebraska all physicians licensed to practice medicine are required by law to register with the Department of Public Welfare annually on or before October 1 and to pay a fee of $1.00. The license expires if the licentiate fails to register, but the license may be revived by the payment of the registration fee and a penalty of $1.00 within thirty days immediately after expiration.

Dr. Elihu S. Wing, F.A.C.P., Providence, has been made President-Elect of the Rhode Island Medical Society.

Dr. Ernest D. Hitchcock, F.A.C.P., Great Falls, Mont., as Chairman of Region 18, Montana and Wyoming, of the War-Time Graduate Medical Meetings, has conducted Graduate Conferences of two days' duration each at the Base Hospital, Fort Francis E. Warren, Cheyenne, Wyo., and at the Base Hospital at Great Falls, Mont. Subjects covered included anesthesia, clinical psychiatry, dermatology, radiology, and physical therapy. The faculty included Lieutenant George A. Bradasch, M.C., U. S. Army, Dr. Charles A. Rymer of the University of Colorado School of Medicine, Dr. Chester North Frazier, F.A.C.P., of the University of Texas Medical School, Dr. Leo G. Rigler of the University of Minnesota Medical School, and Dr. Frank H. Krusen, F.A.C.P., of the Mayo Foundation.

SPECIAL NOTICES

The Board of Trustees of the University of Illinois have announced the acceptance of a grant of $25,000 a year for three years made by The Upjohn Company of Kalamazoo, Michigan, to be devoted to the academic study of the structural composition and possible synthesis of penicillin.

The Company's present grant, says F. W. Heyl, Ph.D., Vice President and Director of Research, provides for an enlarged three-year research chemistry project under the direction of Professor Herbert E. Carter of the department of biochemistry at Urbana, Illinois. This, says Heyl, amplifies both an earlier coöperative research project at that school and the bacteriological and other research which is being conducted at the Company's laboratories at Kalamazoo.

Dr. Carter is well known for his brilliant work with the amino acids, especially the identification and synthesis of the new essential amino acid, threonine, and more recently for his investigations on the structure of the cerebroside sphingomyelin.

The production of penicillin by the natural growth of the mold *Penicillium notatum* is one of the most laborious and unsatisfactory methods in use for the manufacture of any known therapeutic agent. The hope of the future for the large scale economical manufacture of this important drug lies in the solution of the pure chemistry

which alone would lead to the chemical synthesis of the substance. It is in the hope of achieving this end that the Upjohn penicillin fellowship at the University of Illinois has been established.

This grant of The Upjohn Company is a good example of the greatly increasing scientific progress being made today in the chemical and pharmaceutical industries. It indicates the kind of investment in coöperative scientific research that must be made from time to time by leading organizations in these fields.

BETHUNE INTERNATIONAL PEACE HOSPITAL IN CHINA'S NORTHWEST MOVES THREE TIMES IN PAST YEAR TO ESCAPE JAPANESE. The Bethune International Peace Hospital, operating in China's guerrilla Northwest Territory, has been forced to move three times this year, according to a recent report from Mme. Sun Yat-sen to China Aid Council of United China Relief.

This hospital was driven out of its former permanent base at Wutaishan, in northern Shansi Province, in 1941, and since then has always been set up close to the fighting fronts, defying the sporadic Japanese mopping-up campaigns. Mme. Sun's report gives the hospital's present location as western Hopei Province, where it operates in scattered mud and brick peasant huts. This province is nominally "occupied" by the Japanese.

During the past six years, several International Peace Hospital doctors and nurses have lost their lives, but it is the boast of the hospitals' staffs that to date no patient has been lost or abandoned to the enemy.

This record is in part due to the volunteer-assistance of a permanent organization set up by local peasants in the Northwest and placed at the disposal of the guerrilla armies and the four International Peace Hospitals.

When approaching Japanese make hospital evacuation necessary, all resources of the surrounding villages are mobilized: horses, carts, carriers and stretcher bearers. Accompanied by nurses, the "convoys of wounded" are carried by primitive stretchers in relays from village to village. Branches of the peasant organizations meet them at each stop.

Village peasants also give valuable aid to the mobile medical and surgical units which go to within one half-hour's travel from the scene of fighting. Peasants help doctors to prepare operating arenas, set up sterilizing equipment, and to build temporary matsheds to shelter the wounded.

Women in the villages set up food kitchens and prepare dressings under the trained nurses of the medical unit.

Mme. Sun's report to the Council points out that more medical and surgical units are urgently needed. In the last period of active fighting, one mobile unit serviced three regiments, and handled as many as 300 cases of wounded a day. Mobile units can be maintained for $600 a year.

United China Relief, which financially aids the International Peace Hospitals, is a member agency of the National War Fund.

SELMAN FIELD, Monroe, La.—Capt. James O. Finney, chief of medical service at the Selman Field Station Hospital, has been promoted to the rank of major.

Major Finney was graduated in 1929 from Vanderbilt University and in 1933 from the university's medical school.

A native Alabaman, he resided at 509 Reynolds St., Gadsden, Ala., until he entered his current tour of active duty July 14, 1942. For six years he had practiced internal medicine in the Guice-Morgan Clinic in Gadsden.

Major Finney's military career began in Vanderbilt Medical school, where he was an ROTC student. He was commissioned in the Medical Reserve Corps when

he received his medical degree. He took his houseship in Vanderbilt University Hospital, at Nashville, Tenn., and did a year's postgraduate work at the University of Chicago. Then followed a five month tour at the Station Hospital at Ft. McClellan, Ala., after which the major began his practice in Gadsden.

A fellow of the American College of Physicians and a diplomate of the American Board of Internal Medicine, Major Finney has published several articles in the Journal of the American Medical Association, the Annals of Internal Medicine, the Southern Medical Journal and the Journal of the Alabama State Medical Association. Two of his papers have been reviewed in the International Medical Digest.

In 1934, Major Finney married the former Miss Margaret Pride, of Florence, Ala. The Finneys have two children.

Upon reëntering active duty in July, 1942, Major Finney spent a month as ward surgeon in the Station Hospital at Maxwell Field, Ala., and then was transferred to Selman Field.

A. C. P. Regional Meeting, North Central States

On October 16, the North Central States, including Illinois, Indiana, Iowa, Michigan and Wisconsin, held one of the outstanding regional meetings that it has been the fortune of the College to conduct anywhere. The formal program arrived too late to publish in the September Annals, but it is hereunder printed as a model program appropriate for these times.

Program

LeRoy H. Sloan, M.D., F.A.C.P.
Governor for Northern Illinois

Willard O. Thompson, M.D., F.A.C.P.
Chairman, Program and Arrangements Committee

Saturday, October 16, 1943

Morning Session—8:30 a.m.

Ballroom, Drake Hotel

Presiding Officer

Cecil M. Jack, M.D., F.A.C.P., Decatur
Governor for Southern Illinois

"The Application of Graphic Training Aids to Medicine."
Ford K. Hick, M.D., F.A.C.P., Lieutenant Colonel, (MC),
U. S. Army, Chicago, Ill.

"Medical Experiences with the Navy in the Atlantic, Pacific and Caribbean."
James W. Sours, M.D., F.A.C.P., Lieutenant Commander, (MC),
U.S.N.R., Medical Officer V–12 Unit, Illinois Institute of Technology,
Chicago, Ill.

"The Five-Day Treatment of Early Syphilis."
Herbert Rattner, M.D., Assistant Professor of Dermatology,
Northwestern University Medical School, Chicago, Ill.

"Effort Syndrome in Soldiers."
Robert M. Moore, M.D., F.A.C.P., Clinical Professor of Cardiology,
Indiana University School of Medicine; Governor for Indiana,
American College of Physicians; Indianapolis, Ind.

"Personal Experiences in New Caledonia with Special Reference to Malaria."
JAMES E. MCFARLING, M.D., Captain, (MC), U. S. Army, Operations and Training Office, Camp Grant, Ill.

"Some Interesting Aspects of the 1943 Epidemic of Poliomyelitis."
S. O. LEVINSON, M.D., Chairman of Advisory Committee on Infantile Paralysis, State of Illinois Department of Health, Chicago, Ill.

"Recent Advances in Chemotherapy with Special Reference to Penicillin."
WILLIAM BARRY WOOD, JR., M.D., Professor and Head of the Department of Medicine, Washington University School of Medicine, St. Louis, Mo.

INTERMISSION

Presiding Officer

B. F. WOLVERTON, M.D., F.A.C.P., Cedar Rapids

Governor for Iowa

"Recent Advances in the U. S. Public Health Service."
FRANK V. MERIWETHER, M.D., Medical Director, District No. 3, U. S. Public Health Service, Chicago, Ill.

"Some Clinical Observations on Meningococcic Infection."
F. DENNETTE ADAMS, M.D., F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, Consultant in Medicine, Fourth Service Command, Atlanta, Ga.

"Trauma to the Abdomen."
WILLIS GATCH, M.D., F.A.C.S., Dean, Indiana University School of Medicine, Indianapolis, Ind.

"Functional Heart Murmurs."
N. C. GILBERT, M.D., Professor of Medicine and Head of the Department, Northwestern University Medical School, Chicago, Ill.

"Personal Experiences in New Guinea."
LEON S. EAGLEBURGER, M.D., Lieutenant Colonel, (MC), U. S. Army, Medical Field Service School, Carlisle Barracks, Carlisle, Pa.

"Overseas with the Navy and Marines." (Illustrated by two short films.)
(1) "The Medical Department in Amphibious Assault."
(2) "Guadalcanal."
WARWICK T. BROWN, M.D., Captain, (MC), U. S. Navy, First Marine Division, Bureau of Medicine and Surgery, Washington, D. C.

LUNCHEON

12:30 p.m.

Gold Coast Room, Drake Hotel

Presiding Officer

ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Madison

Governor for Wisconsin

"Aviation Medicine."
DAVID N. W. GRANT, M.D., F.A.C.S., Brigadier General, (MC), Air Surgeon, U. S. Army Air Forces, Washington, D. C.

AFTERNOON SESSION—2:00 p.m.

Ballroom, Drake Hotel

Presiding Officer

ROBERT M. MOORE, M.D., F.A.C.P., Indianapolis

Governor for Indiana

"Recent Observations of Practical Significance on Gastric Secretion."
ANDREW C. IVY, M.D., F.A.C.P., Professor of Physiology, Northwestern University Medical School, Chicago, Ill.; Consultant in Naval Medical Research Institute, Bethesda, Md.

"Clinical Disturbances of the Pituitary."
EDWARD H. RYNEARSON, M.D., F.A.C.P., Assistant Professor of Medicine, Mayo Foundation, University of Minnesota; Consultant in Medicine, Mayo Clinic, Rochester, Minn.

"Classification of Hypo-estrinism."
FULLER ALBRIGHT, M.D., Associate Professor of Medicine, Harvard Medical School, Boston, Mass.

"Medicine Overseas."
HUGH J. MORGAN, M.D., F.A.C.P., Brigadier General, (MC), U. S. Army, Professional Service Division, Office of the Surgeon General, Washington, D. C.

INTERMISSION

Presiding Officer

P. L. LEDWIDGE, M.D., F.A.C.P., Detroit

Acting Governor for Michigan

"The Management of Carcinoma of the Colon and Rectum."
JOHN DE J. PEMBERTON, M.D., F.A.C.S., Professor of Surgery, Mayo Foundation, University of Minnesota; Head of Section in Surgery, Mayo Clinic, Rochester, Minn.

"War Neuroses."
DAVID SLIGHT, M.D., Professor of Psychiatry, University of Chicago, The School of Medicine, Chicago, Ill.

"Some Aspects of the Diagnosis and Therapy of Hypochromic Anemias."
OVID O. MEYER, M.D., F.A.C.P., Associate Professor of Medicine, University of Wisconsin Medical School, Madison, Wis.

The evening program included cocktails and a dinner meeting at which Dr. LeRoy Sloan, General Chairman, acted as the Toastmaster. The list of distinguished guests included official envoys from the offices of the Surgeons General of the Army, Navy and Public Health Service, of the Air Surgeon of the Army Air Forces, of the Deans and Professors of Medicine of the medical schools in the territory, of the Associate Directors of the American College of Surgeons, of the Editor of the Journal of the American Medical Association, of the Secretary of the Council on Medical Education and Hospitals of the American Medical Association, of the Presidents of the Institute of Medicine of Chicago, the Chicago Medical Society, the Chi-

cago Society of Internal Medicine, and the Illinois State Medical Society, of the Commanding Officers of the Ninth Naval District, the Great Lakes Naval Hospital, the Station Hospital at Fort Sheridan, the Sixth Service Command, and of the Office of Procurement and Assignment of the Sixth Service Command, as well as many other distinguished physicians and military officers. Brief addresses were made by Dr. Ernest E. Irons, President-Elect of the College, Dr. Charles Hartwell Cocke, 1st Vice President of the College, Mr. E. R. Loveland, Executive Secretary of the College, Commander Edward L. Bortz, Chairman of War-Time Graduate Medical Meetings, Dr. Morris Fishbein, and others.

OBITUARIES

DR. ORVILLE HARRY BROWN

In the death of Dr. Orville H. Brown of Phoenix, Ariz., which occurred in Arcadia, Calif., at the home of his daughter, one of the leading medical figures of the Southwest passed from the scene. For three years friends had witnessed with sympathetic astonishment his heroic struggle against the insidious and inevitable advance of a diffuse malignancy originating in the prostate. Dr. Brown's calm and philosophic acceptance of the situation is well illustrated by a personal report of his case, published in the Urologic and Cutaneous Review for June, 1942. In this attitude he was supported by the constant encouragement of his wife and daughter, as they together faced the situation with open eyes, but with courage and fortitude.

Dr. Brown was born in Kansas, July 18, 1875, and had, therefore, just passed his sixty-eighth birthday at the time of his death. He graduated from the University of Kansas, and then became assistant in physiology in that School for the years 1901 and 1902. He took part of his medical training at the University of Chicago while serving there as assistant in physiology from 1902 to 1904. He then went to St. Louis University School of Medicine, where he was assistant professor of pharmacology from 1904 to 1907, taking his degree in medicine there in 1905. In the same year he received his degree of doctor of philosophy from the University of Chicago.

From 1905 to 1907 he was associate director of the Mount St. Rose Sanatorium in St. Louis, and then became medical director of the Missouri State Sanatorium for Incipient Tuberculosis, at Mt. Vernon, Mo., which position he held from 1907 to 1910. During this period he made several notable contributions to the study of tuberculosis, both from the standpoint of individual treatment and from the aspect of public health. From 1910 to 1916 he was assistant professor of medicine at St. Louis University. During this period Dr. Brown carried out his study and research on asthma which culminated in the publication of his well known book on that subject in 1917, by C. V. Mosby Co.

In 1916, Dr. Brown moved to Phoenix where he spent the remainder of his professional life. For a time he was associated with Dr. W. O. Sweek

as the internist of a medical-surgical team. In 1918 he was appointed Superintendent of Public Health for Arizona, holding this position until 1920. For approximately ten years, between 1920 and 1930, Dr. Brown practiced alone and became established as one of the leading internists of Arizona, giving special attention to asthma, in which field he was an acknowledged authority. In 1930 he formed an association with Dr. Loren C. Barlow, a surgeon, this affiliation being terminated suddenly by the death of Dr. Barlow in June, 1931, from epidemic meningitis. In 1932 Dr. W. L. Reid came as the surgical member of the Phoenix Clinic which was organized by Dr. Brown. Misfortune again struck when Dr. Reid was killed in an automobile accident in 1937.

He was an important figure in the Arizona State Medical Association and the Southwestern Medical Association. He was Editor of *Southwestern Medicine* from 1935 to 1940. In the Arizona Medical Association he held the important post of Historian for many years. He took this office seriously and devoted to it an enormous amount of time and energy. By untiring search through old newspapers and journals, by persistent correspondence with surviving members of families of doctors who had practiced in Arizona, and by personal interviews at every opportunity, he brought together and placed in the archives of the Association historical data regarding every doctor who has ever practiced medicine in the state. It was his ambition to prepare a "Medical History of Arizona," but this task now awaits the attention of some one else. Dr. Brown was elected to Fellowship in the American College of Physicians in 1931 and subsequently became a Life Member. He was a diplomate of the American Board of Internal Medicine, member of the American College of Chest Physicians, the American Association of Biological Chemists, and of the Royal Society of Medicine of London. He was the author of two books: one on "Laboratory Physiology" published during his early years in St. Louis, and the book on "Asthma" (previously mentioned), published in 1917. Besides these books he was the author (in a few instances in collaboration with others) of no fewer than eighty-five medical articles. His last published contribution was the personal account of his terminal illness,—"Two Years Experience With Bone Cancer."

Early in 1937, after the rather sudden development of urinary obstruction Dr. Brown had a transurethral resection done in Los Angeles and in the tissue removed evidences of prostatic carcinoma were found. He elected to be treated by the supervoltage x-ray equipment at the California Institute of Technology. The results seemed to be good and he continued his work. In 1939 the development of back pains, headaches and other symptoms led to investigation and he was found to have a very widespread metastatic involvement of osteoplastic type, in skull, spine, pelvis and ribs. Realizing the inevitable outcome of the situation Dr. Brown closed his office in June, 1940, and went with his wife to live with their daughter and son-in-law in Arcadia, Calif. With the spirit of a true scientist and philosopher, he offered

his case with its dramatic bone lesions, involving every vertebra in the spine and every rib, to the University of California for experimentation with irradiated heavy metals produced by the cyclotron. Under this treatment with irradiated strontium and phosphorus, much interesting and important data were acquired. Through the effect of this treatment, plus occasional treatments in Los Angeles by x-ray for pain, and his own personally directed dietary regimen, his life was prolonged from the maximum of three months set by Phoenix consultants (including the writer), to more than three years. During all this time Dr. Brown maintained his interest in professional work, writing several articles, reading many books and preparing book reviews for Southwestern Medicine, as well as making an intensive study of his own case.

His wife and daughter, facing the situation with equal courage, helped him maintain his cheerful and courageous philosophy to the end, when, undefeated and unafraid, he "wrapped the drapery of his couch about him and lay down to pleasant dreams." He was a good soldier. He fought a good fight. He kept the faith. Nothing better can be said of any man.

W. WARNER WATKINS, M.D., F.A.C.P.,
Phoenix, Ariz.

DR. ROBERT TITUS PHILLIPS

Dr. Robert Titus Phillips (Associate) was born in Boston, Mass., September 15, 1901, and died in a Japanese prison camp in the Philippine Islands, June 11, 1943; aged, forty-one.

He attended the Governor Dummer Academy, received his A.B. degree from Bowdoin College in 1924, attended the University of Edinburgh, Scotland, for one year, returning to Tufts College Medical School, from which he received his medical degree in 1932. He was an intern in 1932–34, and a resident physician from 1934–35, at the Boston City Hospital. Thereafter, he spent another year in residency at the Robert B. Brigham Hospital in Boston. He served as instructor in medicine at Tufts College Medical School, 1935–39; Junior Visiting Physician, Boston City Hospital, 1936–39; and as Assistant Physician at the Robert B. Brigham Hospital, 1936–39. He then removed to Portland, Maine, where he became a member of the staff of the Main General and Children's Hospitals.

Soon after the outbreak of World War II, he entered the Medical Corps of the U. S. Army as Captain. He was stationed in the Philippine Islands and was taken a prisoner of war at the fall of Corregidor. He was promoted to Major while a prisoner of the Japanese.

Dr. Phillips was a member of the Massachusetts Medical Society, the American Medical Association, the American Rheumatism Association, the American Congress of Physical Therapy, the New England Physical Therapy Society and the William Harvey Society. He had been an Associate of the American College of Physicians since 1937.